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13. ABSTRACT *(Maximum 200 Words)*

The Center for Innovative Minimally Invasive Therapy (CIMIT), is a consortium of nonprofit Massachusetts-based institutions led by Massachusetts General Hospital and includes Brigham and Women's Hospital, Massachusetts Institute of Technology and Draper Laboratory. The primary aim of the Center is to develop technologies that will advance the capability of modern medicine to diagnose and treat patients using minimally invasive and less costly approaches. CIMIT will coordinate and implement research programs in cardiovascular disease, cancer, stroke, trauma and critical care, that are supported by basic science and engineering development in biomaterials, endoscopic tools, energy delivery, intelligent decision systems, medical imaging, micro-sensors, outcomes, robotics and simulation. A unique military/civilian partnership fostered by CIMIT will allow DOD technologies to be evaluated by CIMIT investigators and facilitate the transfer to the military of successful minimally invasive approaches developed at CIMIT. An educational program, which includes coursework, seminars, and on site training opportunities, will serve the shared needs of academic and military physicians and scientists. The overall goal of CIMIT is to create a national program that combines clinical and technological excellence in order to generate, develop, and reduce-to-practice innovative and high-impact concepts in minimally invasive therapy.

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James E Muller MD 26 Oct 00

SIGNATURE DATE

Table of Contents

Executive Summary

This report covers the period October 1, 1999 - September 30, 2000, the second year of CIMIT operation under DoD funding. CIMIT is a non-profit consortium of world-leading academic and research institutions founded by Partners HealthCare System, Massachusetts General Hospital, Brigham and Women's Hospital, Massachusetts Institute of Technology, and the Charles Stark Draper Laboratory.

CIMIT's mission is: *"To improve patient care by bringing together scientists, engineers, and clinicians to catalyze development of innovative technology, emphasizing minimally invasive diagnosis and therapy."*

A major goal of CIMIT is to provide new medical technology of value to the Department of Defense. Special emphasis is given to development of technology to improve the care of combat casualties.

The use of technology has revolutionized health care; and the capabilities now being developed have the potential to make even more dramatic changes. While the explosive growth in areas such as imaging, robotics, fiber optics, high-speed computing and biomedical engineering have demonstrated vast potential for medical use, the challenge of successfully taking these technologies from bench to bedside remains.

CIMIT was started in 1994 to address this challenge, with seed funding from philanthropy and the Massachusetts General Hospital. CIMIT received major federal funding through the Department of Defense beginning in 1998. The CIMIT Programs have been:

Clinical Focus Areas: (CFAs)	Cardiovascular Disease	Cancer	Stroke
	Trauma and Critical Care	New Initiatives	

Advanced Technology Teams (ATTs)

Technology Assessment and Outcomes Analysis

Through DoD's support, CIMIT has assembled a superb team of clinicians, scientists and researchers to lead its scientific programs and a management team with experience and expertise in operations, technology development, and program management. CIMIT also supplies mechanisms to facilitate technology transfer and ultimate application to patient care. Programs in Technology Development, Industry Collaboration, Regulatory Affairs, and Education have been developed to facilitate its work.

CIMIT catalyzes collaborations that are monitored, measured, and analyzed for their ultimate application in acute care in the field, as well as in the clinical setting. These innovative projects would not have occurred in a traditional environment. CIMIT has delivered significant results in all its programs, and is well positioned for even greater accomplishments.

CIMIT Year 2 DoD Expenditures

This chart shows total rounded expenditures by activity area corresponding to the sections of this report. Expenditures for the Stroke CFA and Image Guided Therapy ATT include significant funds budgeted in Year 1 but expended during year 2.

Project Areas	$ (000) Expended
2.0 Clinical Focus Areas (CFAs)	
2.1 Cardiovascular Disease	690
2.2 Cancer	485
2.3 Stroke	645
2.4 Trauma and Critical Care	460
2.5 New Initiatives	100
3.0 Advanced Technology Teams	
3.1 Biomaterials	360
3.2 Image Guided Therapy	150
3.3 Microsensors	855
3.4 Simulation	1410
3.5 Tissue Engineering	2640
4.0 Technology Assessment & Outcomes Analysis	800
5.0 Core Activities	
5.1 Education	307
5.2 Regulatory Affairs	43
5.3 Industrial Collaboration	160
5.4 National CIMIT	40
5.5 Technology Development	265
6.0 CIMIT Operations	1020
Total	10430

1.0 Introduction

1.1 Background

CIMIT was created in 1994 by MGH physicians with the conviction that high technology could be better utilized to improve patient care. The initial work was supported by the hospital; it was predominately clinical in focus, with limited central or core activities. To solidify working relationships, provide a central leadership capability and establish a wider research base, the CIMIT Consortium was formed, and DoD support was solicited in 1998.

Research has been divided into two thematic categories: Clinical Focus Areas (CFAs) and Advanced Technology Teams (ATTs), and mechanisms such as the CIMIT Forum were set up to stimulate collaboration. The importance of the military healthcare mission was recognized, and collaborations with military staff were initiated. The well-established process of physician leadership for the major programs was maintained. Research in the first two years has been directed toward the major clinical challenges: Cardiovascular Disease, Cancer, Stroke, and Trauma, and a variety of attractive technologies.

By the end of the first year, the opportunities for the unique role and contribution to be made by CIMIT were clear. Two major activities were initiated: (1) To refocus and recommit the CIMIT community (accomplished though a series of working sessions in the latter half of Year 2), and (2) To establish an Operations Committee formed of experienced leaders in successful medical technology development. The mission statement now reads:

"To improve patient care by bringing together scientists, engineers, and clinicians to catalyze development of innovative technology, emphasizing minimally invasive diagnosis and therapy."

While CIMIT's range of application has broadened (as reflected in the recent change of name to Center for the Integration of Medicine and Innovative Technology), the approach has sharpened, to best leverage the extensive research at the collaborating institutions. Criteria for supporting Projects are:

- The work meets peer review metrics for uniqueness, quality, and contribution.
- The Project is multi-disciplinary, and preferably multi-institutional, outside of the normal academic patterns of collaboration.
- There is an apparent, if not immediate, path to clinical or Combat Casualty Care impact, including the steps beyond the period of CIMIT support.
- If successful, the work will advance the field significantly toward the long-term goals.
- CIMIT's non-financial resources (synergy, core programs, leadership, mentoring) will add value.

The role of CIMIT may be understood by referring to Figure 1, which outlines the pathway from a new concept to successful clinical use. CIMIT works in concert with the primary Commercial, Clinical, and Societal activities, providing enabling resources and expertise along the pathways and through the interactions to best position the work for success.

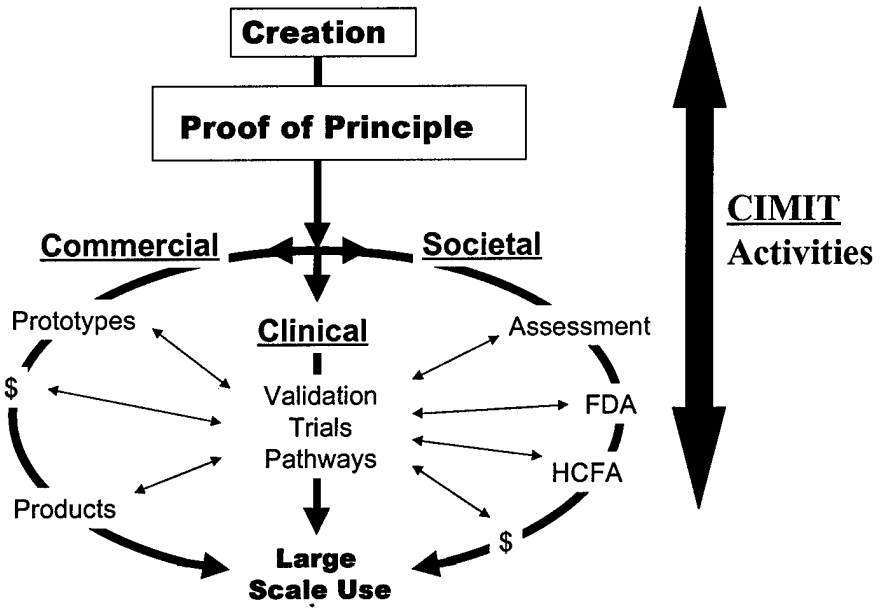


Figure 1: Schematic of the Pathways of Medical Develpoment in the US.

It became clear in the first year that strong, committed clinical champions were needed to lead CIMIT programs, due to the required project scale and the broad professional attitude required to accept and adopt new approaches. Three of the ongoing Program Leaders (Dr. Muller in Vulnerable Plaque, Dr. Vacanti in Tissue Engineering, and Dr. Oesterle in Endovascular Devices) were recruited to the MGH and to CIMIT to establish those programs. Also in that period, the Education and the Outcomes Assessment programs were begun to assist investigators, and the Industrial Collaboration activities established to provide linkages for commercialization and shared development.

CIMIT has thus evolved and grown, while preserving its core commitment to promote the adoption of technologies to address unmet healthcare needs. The ongoing programs are strong, and all have recorded significant accomplishments in the past year. There are several examples of project evolution beyond CIMIT, into commercialization or larger scale sponsored research. CIMIT has mechanisms for self-renewal and capacity for growth, which will ensure its long term success.

1.2 Research Organization

The CIMIT research agenda is driven by clinical needs and supported by innovative technology development. This approach enables the identification of key medical problems, the selection of appropriate new procedures and the assessment of the cost efficacy throughout the continuum from concept to ultimate clinical impact of new products and/or procedures. CIMIT has coordinated and implemented minimally invasive programs in five key Clinical Focus Areas (CFAs): Cardiovascular Disease, Cancer, Stroke, Trauma and Critical Care and New Initiatives. CFA leaders have responsibility for:

1. Identification of novel minimally invasive technologies and procedures from internal and external sources,
2. Management of their development through a continuum extending from basic to clinical research,
3. Monitoring the progress of their projects.

These CFAs are supported by basic science and engineering development teams called Advanced Technology Teams (ATTs), organized at the beginning of the year in these groupings: biomaterials, endoscopic tools, energy delivery, intelligent decision systems, medical imaging, miniaturized sensors and devices, simulation, modeling, robotics, surgical planning, tissue engineering and endovascular tools. Over the course of the year, as described in Section 3.0 below, the content of the ATTs was restructured. The ATTs provide access to a tremendous infrastructure of enabling technologies from MIT and Draper Laboratory in such areas as micro-devices, artificial intelligence, control systems, physics-based simulations, and robotics and are anticipated to contribute to multiple CFAs depending on needs. This structure will not only support an active vertical communication network but also facilitate the development of "dual application" technologies that are useful across clinical disciplines.

The CIMIT research program is modeled after the NIH "program project" mechanism where a team of clinical and basic scientists utilizes appropriate core capabilities to address key medical problems synergistically. The team can identify potential new technology, test the device or procedure in model systems, provide technology assessment at an early stage, perform clinical research and analyze the outcome of the procedure. CIMIT has evolved the strategy of developing "projects into programs". A major value of CIMIT is to produce coordinated research evaluating various approaches to the continuum of care for a disease entity. The approach results in overall improved care or decreased morbidity and mortality, that would not have been as great had each project been researched individually, or not evaluated in relation to the entire episode of care.

During the past year, Technology Assessment and Outcomes has expanded from an ATT to a critical component for all CIMIT research. The principal activities of the program will be the development and application of rigorous scientific methodologies – particularly cost-benefit and cost-effectiveness analysis, decision analysis, and outcomes analysis. The specific objectives of the program are to: 1) focus the allocation of resources for the development of new diagnostic and therapeutic technologies, 2)

facilitate rapid and accurate assessment of their efficacy, and 3) clearly demonstrate their value to the public, physicians, payers, and the legislature. The program provides an infrastructure and the expertise to properly evaluate minimally invasive diagnostic and therapeutic procedures at all stages of development, particularly during the early stages from discovery to preliminary clinical testing, when extensive data regarding clinical effectiveness may not yet be available. In these instances, computer models will be utilized to simulate expected costs and outcomes, and thereby help focus the development process. The program also provides the expertise to evaluate new procedures as they move into clinical practice, building robust condition-specific databases that will facilitate comprehensive analysis of clinical effectiveness.

1.3 Major Accomplishments

Clinical Focus Areas:

- Demonstrated efficacy of novel tissue sealant applied to the anastomosis of minimally invasive coronary bypass procedure in a large animal model;
- Demonstrated utility of Zeus Robotic Surgical System and Heartport cardiopulmonary bypass techniques in large animal model;
- Developed a small animal model for activation of endothelial cells in the lining of the cardiovascular system:
- Demonstrated optical techniques to detect early hemorrhage and continuously monitor brain hemodynamics;
- Developed innovative techniques to diagnosis and treat acute stroke;
- Developed animal model for proton beam treatment of intractable epilepsy;
- Demonstrated image-guided focused ultrasound to treat cancer;
- Development and application of novel Optical Coherence Tomography (OCT) techniques to detect vulnerable plaque in blood vessels and abnormal tissue in the GI tract;
- Optical techniques to determine tissue and organ status (pH, pO2, pCO2) in trauma and critical care settings;
- Developed lung volume reduction techniques for treatment of emphysema; and
- Developed computer-based, three-dimensional image treatment planning system for endoscopically placed distraction device.

Advanced Technology Teams:

- Development of a polymer-based gene delivery platform;
- Design, fabrication and testing of a 3-dimensional culture system for tissue engineering;
- Developed image-guided, segmentation techniques based on adaptive filtering;
- The simulator system developed jointly by CIMIT and Mitsubishi for fluoroscopic catheterizations is now being used commercially by Guidant for customer training.
- Development of a micro-electro-mechanical silicon (MEMS) platform for bioassay;
- MEMS may be used for:
    - predicting multiple organ failure (MOF);
    - measuring blood components;
    - pathogen detection;
    - development of novel approaches for tissue engineering.
- Development of animal models for minimally invasive meniscal repair;

Technology Analysis and Outcomes Assessment:

- Stroke CFA: Established database with over 7,000 patients treated for cerebrovascular disease. This data base can be used for cost/benefit analysis of stroke treatment.
- Image Guided Therapy Program: Completed a cost-effectiveness analysis for surgical resection of liver metastases, Analyzed the benefit of Optical Coherence Tomography in upper gastrointestinal disorders.

1.4 Care of the Combat Casualty

CIMIT investigators and leaders place special emphasis on the care of the combat casualty, as exemplified by the efforts in each of our major scientific proposals: The Simulation ATT and Trauma and Critical Care CFA are directed toward these needs. Tasks in other CIMIT Programs, such as the Telestroke Task or the growth of replacement organs through the Tissue Engineering ATT, involve development of technologies and applications that will support CCC requirements. More broadly, it is expected that new devices, techniques, and procedures developed in the Image Guided Therapy ATT and various CFAs (hemorrhage control, more efficacious general surgery) will find application in CCC. Here are some specific activities:

Simulation ATT Under the general leadership of the DoD's Medical Simulation Trainer Initiative (MSTI), CIMIT is taking a lead role in developing both the core technology and enabling applications to support training the combat medic and other military acute care personnel. Particular thrusts are in the development of tissue modeling approaches and high level software to enable more realistic and cost effective procedure simulators to be deployed. This work is complemented by a planned series of annual technology readiness (pre-prototype) demonstrations.

Trauma and Critical Care CFA This program is directed toward developments to directly support combat casualty care. Primary projects are:

- Assessing the Severity of Hemorrhagic Shock
- RAFTS: A Fieldable Device to Support Triage Decisions

In the **Microsensors ATT**, the MEMS Device for Real-Time Blood Assay may yield significant benefits for mnonitroinbg patients in post surgical trauma.

Telestroke Task The management of acute stroke is a significant problem in the general population, including the deployed military. The principal benefit to combat care will be in the demonstration of cost effective and reliable large scale systems for remote diagnosis and staging of stroke and cranial trauma.

Tissue Engineering ATT This activity is establishing a platform technology to improve the care of the wounded soldier. The program will address the organ shortage and massive tissue defects by providing the technology to create optimized living replacement structures for:

- Structural tissue repair including bone, cartilage, and muscle.
- Cardiovascular repair including blood vessel substitutes, heart valve substitutes, and cardiac muscle replacement.
- Neural repair including spinal cord and peripheral nerves.

Novel Interventional Techniques As an example of this work, CIMIT investigators have designed a series of percutaneously delivered aortic balloon catheters that have the potential to stabilize soldiers with penetrating abdominal wounds and life-threatening hemorrhage.

2.0 Clinical Focus Areas

The CIMIT research agenda is driven by clinical needs and supported by innovative technology development. This approach enables the identification of key medical problems, the selection of appropriate new procedures and the assessment of the cost efficacy throughout the continuum from concept to ultimate clinical impact of new products and/or procedures. CIMIT has coordinated and implemented minimally invasive programs in five key Clinical Focus Areas (CFAs) including: Cardiovascular Disease, Cancer, Stroke, Trauma and Critical Care and New Initiatives.

2.1 Cardiovascular Disease CFA

Background and significance

Cardiovascular disease is the leading cause of death in the United States, with the greatest single cause resulting from ischemic heart disease secondary to coronary artery atherosclerosis. The major test for diagnosing the severity of coronary disease is cardiac catheterization, performed approximately 500,000 times per year. Despite this large number of examinations (and concomitant cost), several fundamental parameters cannot be addressed unambiguously using this technique: the volume of myocardium potentially involved in the ischemic process, the severity of ischemia, and characterization of atherosclerotic plaques.

Therapy for incipient occlusion includes approaches to open or bypass the vessel. However, with balloon angioplasty or stenting, there is a high rate of re-occlusion. In addition, many vessels threatened for occlusion have non-significant stenosis and may be missed with the focus guided by lumen diameter. Also, balloon angioplasty does not provide feedback to indicate wall stress, and it is likely that at least part of the high restenosis rate is due to wall injury resulting from the procedure itself. Thoracotomy for bypass certainly is no panacea, and is generally reserved for patients whose lesions are not amenable to catheter-based relief. These patients would benefit significantly if minimally invasive approaches could replace open heart surgery. Furthermore, there are many patients with distal vessel disease whose lesions are not amenable to any current therapy, medical or surgical.

Atherosclerotic disease can also lead to aneurysm formation of both large and small vessels. Current management is open surgery with repair of the defect using various synthetic materials. This costly treatment has significant risks of morbidity and mortality. The development of novel materials and procedures for percutaneous placement of vascular stent grafts should dramatically reduce both the risks and cost of therapy in these patients.

New approaches are required to enhance the treatment of vascular disease. Both diagnosis and therapy need to be directed at the biology of the vessel and individualized

for the particular patient. This require cross-disciplinary expertise in clinical medicine (cardiology, radiology and surgery) and basic science (engineering, physics, biomaterials, etc,) as well as the development of novel approaches including optical imaging and spectroscopy, ultrasound, hydraulics, photobiology, and catheter design. All areas of expertise are present in the CIMIT consortium.

Task 1: Detection of Vulnerable Plaque using Optical Coherence Tomography

Introduction

A multi-disciplinary multi-institutional effort is underway to detect and treat vulnerable plaque using innovative noninvasive (CT, MRI) and intravascular (OCT, MRI, IVUS) approaches. These strategies for detection of vulnerable plaque require close interactions among investigators in biology (molecular biology, genetics, etc.), treatment (medical, interventional, etc.) and health service research fields (epidemiology, efficacy, etc.).

The OCT catheter development group's philosophy has been to incorporate OCT imaging capability into an FDA approved IVUS catheter though minimal modification. Development of an OCT catheter based on the Boston Scientific 2.6 F IVUS catheter was completed, however, this catheter model was recalled. A second OCT catheter was developed based on the Boston Scientific 3.2 F, 30 MHz device. This catheter was successfully tested in swine coronaries *in vivo*. The recent release, by Boston Scientific, of a 40 MHz, 3.0 F catheter has allowed development of a third OCT catheter design. This process is underway.

To couple light from the OCT system into the rotating catheter, an optical rotary junction has been developed. The narrow diameter and high angular misalignment sensitivity of standard telecommunications optical fiber posed a significant challenge in the design of such a rotary junction. The current device provides outstanding performance in terms of insertion loss (<0.2 dB), rotational modulation (0.05 dB), and back-reflections (<-50 dB). The device is computer controlled and is compatible with standard IVUS pullback equipment.

A database of OCT images of more than 50 cadaveric vessel segments with corresponding histology has been acquired. From this database, criteria for characterizing atherosclerotic coronary plaques have been identified. Continuing studies will prospectively evaluate the accuracy of these criteria compared with histology.

OCT imaging has been performed in the coronary arteries of five living swine. The mechanical characteristics of the OCT catheter, developed by the team, were compared with those of standard IVUS catheters by two independent cardiologists. No mechanical differences were identified. All three main coronary arteries were imaged in each swine with no OCT related complications.

Specific Aims: To develop, optimize and apply OCT imaging for the detection of vulnerable atherosclerotic plaques in human coronary arteries. To identify OCT

morphologic features that distinguish vulnerable from stable plaques. To determine catheter and imaging characteristics in a porcine model.

Progress:

OCT imaging system:

A narrow diameter (3.2 F) OCT catheter suitable for intravascular imaging *in vivo* was developed. The OCT catheter was constructed using components from an FDA approved IVUS catheter that consists of a single mode optical fiber within a wound stainless steel cable. At the distal tip of the fiber, a gradient index lens and a micro prism were used to produce a focused output beam that propagates transversely to the catheter axis. Surrounding the mechanical and optical components was a transparent, sealed plastic sheath. The sheath was designed to incorporate a guide wire in a monorail configuration (Figure 1). All the mechanical properties of the catheter are comparable with the IVUS 3.2F catheter. The scattered light from the surrounding tissue was collected by the same optical system and coupled back to the fiber.

The stainless steel cable that carries the fiber and the focusing optics was cemented to an FC fiber optic connector that could be attached and detached from the rotating end of the rotational coupler (Figure 1). The coupler consisted of two gradient index (GRIN) lens collimators separated by an air gap precisely aligned to assure maximal throughput. A stabilized electrical motor was used to spin the rotating end of the coupler (4-8 Hz) with the catheter through a belt drive. The rotating coupler, the motor, and the drive were enclosed in a compact (12 cm x 5 cm) hand-held unit compatible with the requirements of the cardiology suite (Figure 1). An oral presentation describing the new technical innovations in this catheter was presented at the Optical Society of America Biomedical Topical Meetings (April, 2000).

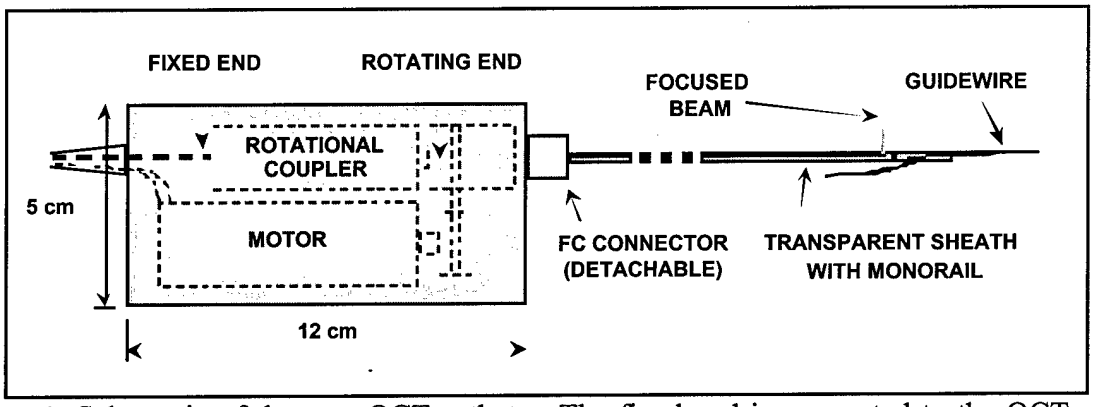


Figure 1. Schematic of the new OCT catheter. The fixed end is connected to the OCT system and the rotating end is connected to the stainless steel cable which rotates the distal optics. The catheter can be easily interchanged via the FC connector.

An OCT system was constructed to interface with the rotating catheter and perform pull-back imaging. The rotational speed of the catheter is carefully controlled by the OCT system for proper image registration. Catheter pullback is performed either manually or under computer control. To accurately display the circular cross-sectional images acquired with the OCT catheter, the system software performs a real-time rectangular to circular spatial transform of the image data. A new broadband optical source, with an

optical power 3 times higher than that in the OCT system previously constructed with CIMIT funding, is used to offset decreased imaging penetration depth while imaging through blood. The entire system is enclosed in a portable cart and is capable of easily being transported within the hospital.

OCT of vulnerable versus stable plaques:

From a total of 80 cadaveric arterial segments imaged in our preliminary study, 42 were coronary artery segments. All segments were marked with a suture through the lumen of the artery and imaged using a 3.2F or 7F OCT catheter with a pullback length of 5 mm. After imaging, the location of the suture was marked by India ink applied to the outer surface of the adventitia. Histologic sections were obtained every 50 μm and stained with either Hematoxylin and Eosin (H&E) or Movat's Pentachrome. OCT images were compared to histology for identification of discrete morphologic parameters. Fibrous cap thicknesses were measured by OCT and histology and the correlation was determined by Pearson's correlation coefficient, *r*.

In all non-atheromatous coronary artery segments (n = 17), differentiation of the intima, media, and adventitia was possible due to differences in backscattering from these layers (Figure 2). In all non-atheromatous segments, the media was less backscattering than either the intima or the adventitia (Figure 2). Since the study population from cadavers was heavily weighted towards advanced age, intimal hyperplasia was identified in all OCT images of the non-atheromatous segments (Figure 2). The internal and external elastic laminas were infrequently identified as discrete morphologic entities. More often, the location of the internal and external elastic lamina could be inferred as the boundary between the anatomic layers of the artery. Absence of a layered structure was seen in all of the coronary arteries with atheroma (n = 25) (Figures 3 - 5). Calcifications within the plaques (n = 11) were identified by the presence of high backscattering at the interfaces between calcification and the surrounding tissue, a low backscattering heterogeneous interior, and increased imaging penetration depth (Figure 4). However, based on these static images, the appearance of many coronary arteries with calcifications is very similar to that of atheromatous plaques with thin caps. Lipid pools (n = 15) were identified by the presence of heterogeneous low backscattering areas (Figure 5). Some images also contained evidence of neovascularization, seen as well-defined areas of low backscattering (vessels) within the lipid core of the plaque (Figure 5). A reliable match between the OCT images and histology was found in 10/25 of the atheromatous specimens. Fibrous caps were measured by OCT (30 - 450 μm) and cap thicknesses correlated well with histology ($r = 0.98$) in the 10 specimens with a reliable OCT-histology correspondence.

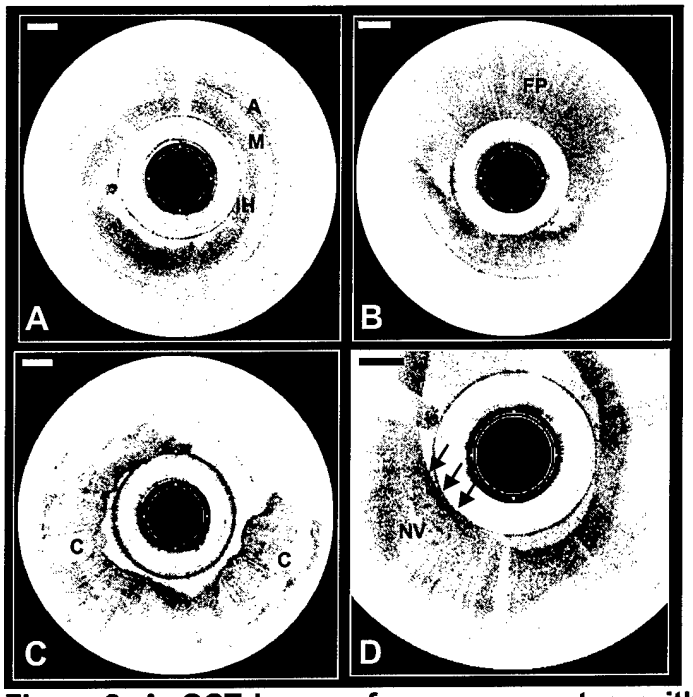


Figure 2. A. OCT image of a coronary artery with intimal hyperplasia (IH). The media (M) and adventitia (A) are also clearly seen. B. OCT image of a coronary artery with a large, eccentric fibrous plaque (FP). C. OCT image showing intimal and medial calcifications (C). OCT image of an atheromatous plaque (P) with a thin fibrous cap (arrowheads). Note the presence of neovascularization (NV) within the lipid core. Scale bars, 500 µm.

OCT imaging and histopathologic correlation of a large number of coronary arteries *in vitro* is an important step that must be performed to understand *in vivo* OCT images of human atheromatous pathology. Our study of 42 coronary artery segments has helped to expand the diagnostic criteria for clinically relevant atheromatous pathology. The presence of a layered structure with a thickened intima and a discrete media and adventitia was characteristic of non-atheromatous coronary arteries. Loss of the layered appearance of the OCT image always correlated with either the presence of calcifications or atheroma. Lipid-rich atherosclerotic plaques with fibrous caps were identified in many of the OCT images and the measurements of cap thickness correlated well with histology. The similarities between many images of calcified coronary arteries and thin capped plaques may present a diagnostic dilemma. However, it is likely that with real-time imaging *in vivo*, the different temporal mechanical dynamics of these two entities will enable their differentiation.

OCT using porcine model:

Normal coronary arteries, intimal dissections, and stents were imaged in five swine with the catheter-based OCT system and compared with intravascular ultrasound (IVUS). Under fluoroscopic guidance, each coronary artery was identified by contrast injection. A guide wire was advanced into each coronary artery and IVUS (30 MHz CVIS, Sunnyvale, CA) imaging was performed. The OCT catheter was then advanced over the guide wire. Visualization of the entire arterial wall was attempted with repeated manual normal saline flushes (8-10 cc bolus) through the guide catheter. The OCT catheter was

then reinserted into all three coronary arteries five times by two interventional cardiologists to test its mechanical properties. An intimal dissection was created using an oversized balloon catheter with high-pressure inflation up to 12 atm (x3) for a duration of 30 seconds. Following angioplasty, IVUS and OCT imaging were repeated. Finally, a 4.0x16mm NIR stent was deployed at 16 atm and imaged by IVUS and OCT.

Four of the five animals survived testing of all three coronary arteries. One swine developed ventricular fibrillation and could not be resuscitated. Post-mortem analysis of this animal revealed no evidence of dissection or thrombus. The likely cause of death was an air embolus. In the other four animals, there was no angiographic evidence of dissection or thrombus formation. The mechanical properties of the OCT catheter were identical to those of the IVUS catheter.

Due to increased optical loss caused by blood interposed between the catheter sheath and the arterial wall, OCT images of the coronary artery obtained without saline purging allowed visualization of coronary artery wall only when the catheter sheath was in close proximity to the tissue (Figure 3A). Clearer visualization of the entire vessel wall was achieved with a saline flush (Figure 3B). Following a purge, the duration of unobstructed imaging ranged from 2-5 seconds. There was no purging-related ventricular arrhythmia. With this purging technique, the intima, media, and adventitia of the coronary artery wall could be easily differentiated (Figure 3B), whereas differentiation of the layered vessel wall structure was not possible with IVUS. Imaging at 4 fps (Figure 1B) showed motion artifacts; imaging at 8 fps reduced the motion artifacts, but with a slight loss of resolution.

While large medial flaps could be identified using IVUS (Figure 3C), OCT images provided visualization of fine structure at the dissection site. Abnormalities including small intimal/medial defects and microscopic flaps could be clearly resolved by OCT (Figure 3C), and were not identified by IVUS. Images of the deployed stent acquired by the OCT system showed the precise relationship between the vessel wall and the stent (Figure 3D). IVUS was capable of imaging struts in the wall, but the relationship between the struts and the surrounding tissue cell layers was difficult to perceive.

In this preliminary experiment, the team has demonstrated that *in vivo* OCT imaging of coronary arteries is feasible and provides images of coronary artery microstructure that are unparalleled by other imaging techniques. OCT images of the normal swine coronary vessels demonstrate the capability to visualize the morphologic layers of the vessel wall with high contrast and spatial resolution. These results, in combination with data from prior *in vitro* OCT studies of atherosclerotic plaques, support the potential role for OCT in the detection of vulnerable plaques. Images of dissections demonstrate the ability of OCT to enable visualization of small alterations of the intima and media that cannot be seen by IVUS. As a result of the high-resolution imaging capabilities of OCT, it may become a more accurate method for assessing the extent of dissections and planning interventional procedures. Finally, OCT images of the deployed stent show that the relationship between the stent and the artery wall can be precisely determined by OCT, opening up the possibility of using OCT as a tool to aid the cardiologist in measuring stent apposition after deployment.

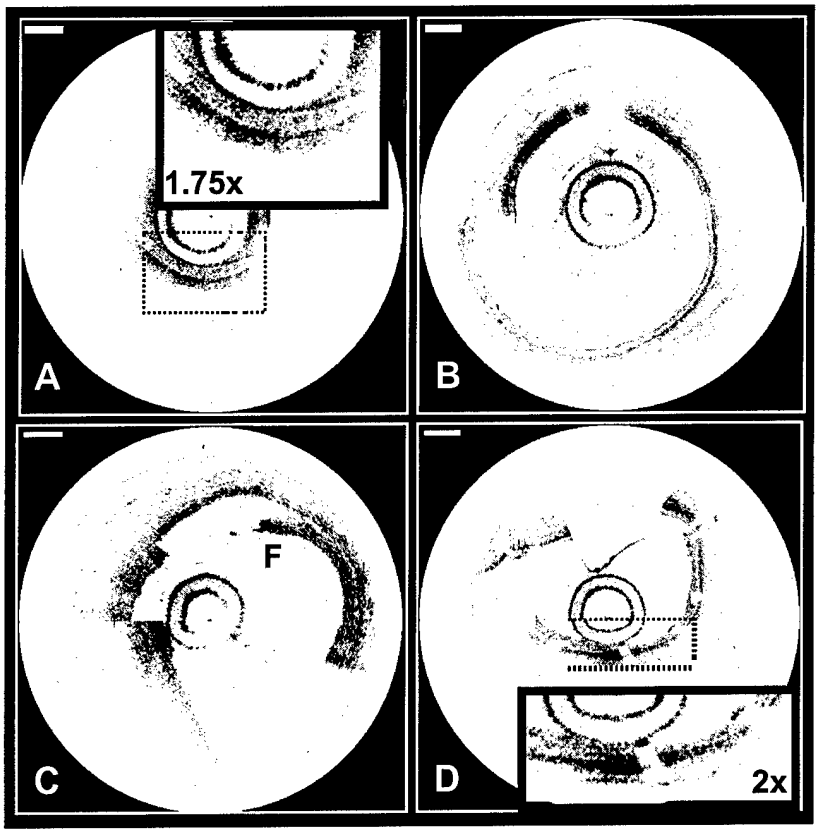


Figure 3. OCT images of the porcine coronary arteries acquired *in vivo*. A. Image obtained without a saline flush allows visualization of the layers of the vessel wall, including the intima (I), media (M) and adventitia (A), only when the catheter sheath is in close proximity to the artery. B. Image acquired during a saline flush enables visualization of the morphologic layers of the entire artery. C. OCT image of a dissection shows fine structure, including a small flap (F) at the dissection site. D. OCT image of the deployed stent allows the determination of the precise relationship between the vessel wall and the stent. Scale bars, 500 µm.

Task 2: Minimally Invasive Cardiac Surgery – Endoscopic Coronary Anastomosis

The overall goal of this project is to develop methods and instrumentation to facilitate endoscopic coronary artery anastomoses ("E-CABG") using a robotic interface ("Zeus", Computer Motion, Inc.). Tissue sealants have been investigated as alternatives and aids to traditional anastomotic methods. Since initiation of the project in June 1999, advancements have been made in instrument port positioning, internal mammary artery cannulation and harvesting, and surgical skill in performing an anastomosis using the robotic interface.

The principal investigator/ cardiac surgeon has used the Zeus Surgical System to perform completely endoscopic LIMA (left internal mammary artery) takedown with LIMA to LAD (left anterior descending artery) anastomoses in forty-six canines. Six RIMA (right internal mammary artery) anastomoses were performed. All completed anastomoses

appeared patent on visual inspection and autopsy. The pre-clinical experience of our lab supports that a robotic interface, used with appropriate methodology and instrumentation, is capable of performing the selected surgical tasks needed for this surgery.

Specific Aim 1: Further characterize FocalSeal surgical sealant as a hemostatic adjunct..

Progress: Previous chronic canine studies have demonstred that FocalSeal surgical sealant is an effective hemostatic adjunct without associated tissue toxicity when applied to blood vessel anastomoses site. This study further characterized the mechanical effects of the hydrophilic sealant on blood vessels. A poster presentation of the *Mechanical Effects of Hydrophilic Tissue Sealant on Blood vessels* was displayed at the International Society for Minimally Invasive Cardiac Surgery in Atlanta, Georgia, June 8-10, 2000.

Specific Aim 2: Perform acute and chronic evaluation of a new micro-anastomotic device on coronary arteries.

Progress: A device to perform proximal graft anastomoses under fluoroscopic guidance is still being developed by St. Jude, Inc. Currently the device is undergoing a final series of tests before it is delivered to the team. The team anticipates the potential use of the device to perform multivessel coronary artery bypasses with minimally invasive techniques.

Specific Aim 3: Develop a method to facilitate video-endoscopic coronary anastomosis. The original intent was to perform manually sutured anastomoses augmented by the use of a surgical sealant. Subsequently, a robotic interface was used to optimize anastomotic technique and much of our efforts have been devoted to optimizing the use of this technology.

Progress: Since the project's initiation, the principal investigator/cardiac surgeon performed 46 E-CABG (endoscopic coronary artery bypass procedures in the canine model using the Zeus Robotic Surgical System and Heartport cardiopulmonary bypass techniques. In 45 of the 46 animals, the left internal mammary artery (LIMA) was harvested using the Zeus system in a completely endoscopic fashion (in one animal the LIMA was harvested by hand through an open sternotomy). Additionally, in six of the 45 animals where Zeus was used for LIMA harvest, the right internal mammary artery (RIMA) was harvested using the Zeus system. Opening of the pericardium and incising of the coronary artery was performed using the Zeus system in 45 procedures.

Creation of the LIMA-LAD anastomosis was attempted in 45 cases, and creation of the RIMA-LAD anastomosis was attempted in six cases. In 42 animals, skeletonization of the distal IMA pedicle was performed using the Zeus system in a closed-chest. In the remaining four animals, the distal IMA pedicle was prepared manually by withdrawing the pedicle through a port in the chest wall.

LIMA and RIMA patency were evaluated by visual inspection and confirmation of adequate blood flow upon brief release of vessel clamp. Two of the 45 harvested vessels were occluded due to trauma sustained from the ultrasonic scalpel. In each completed

anastomosis, patency was verified by visual inspection and autopsy, with angiograms performed in several cases. All completed anastomoses appeared patent.

The completion time for individual surgical tasks was recorded in 23 of the 46 cases. The mean LIMA harvest time with Zeus was 67 minutes (n=23), with a range of 45 to 108 minutes. The mean RIMA harvest time with Zeus was 56 minutes (n=6), with a range of 10 to 86 minutes. Mean time for creation of the LIMA-LAD anastomosis with Zeus was 39 minutes (n=21), with two anastomoses times not recorded), ranging from 24 to 73 minutes. Mean time for creation of RIMA-LAD anastomosis was 37 minutes (n=6). During each procedure, the time spent by the surgeon performing surgical tasks with Zeus ranged from approximately three to six hours.

During these animal studies, two devices have been developed that have proven useful in the lab and may have clinical applicability. One is a novel fiber optic catheter that is used for internal mammary artery visualization and cannulation. The second device is an endoscope lens washing system that improves visualization during mammary artery dissection. Both instruments are under further development with industrial partners to determine appropriateness in the human operating room.

The pre-clinical data supports that the Zeus System, with proper surgical methods and instruments, is suitable for use in endoscopic LIMA harvesting and that the system is capable of performing the selected surgical tasks needed for this surgery.

Future Work Each component of the E-CABG procedure will continue to be optimized in the laboratory and the principal investigator/cardiac surgeon will continue weekly surgical skill training using the robotic interface. The blood flow across the anastomosis site will be studied in animals weaned from cardiopulmonary bypass after successful revascularization, as described in the original proposal. Instrumentation that augments minimally invasive surgery will continue to be developed with industrial collaboration.

In a joint project with Harvard's Department of Engineering, an image-guided program for directing robotic control of internal mammary harvesting is being developed. The plan is to study if this would lead to safer internal mammary artery dissection, since the intraoperative movement of the robotic interface would be linked directly to the anatomical course of the vessel as "mapped out" by the patient's pre-operative CT scan.

Following regulatory approval of the Zeus robotic interface for human use, the laboratory will continue to provide surgical training and serve as a source for methods and instrumentations that improve patient care.

Task 3: Endothelial Activation Markers as Molecular Targets for Innovative, Minimally Invasive Diagnosis and Therapy in Cardiovascular Disease

The endothelial cells (EC) that comprise the lining of the cardiovascular system constitute a dynamically mutable interface in health and disease. In response to various inflammatory, thrombotic and atherogenic pathophysiologic stimuli (e.g., cytokines,

coagulation factors, bacterial and tumor products, advanced glycation endproducts, oxidized lipoprotein components, injurious agents, biomechanical stresses), EC can undergo phenotypic modulation to a dysfunctional state that is marked by expression of "activation antigens", such as E-selectin (ELAM-1) and VCAM-1 (Athero-ELAM). The detection of soluble/shed forms of these cell surface markers in serum/plasma is already being utilized as a surrogate index of endothelial dysfunction in certain clinical studies. The team proposes to further exploit these EC phenotypic markers as molecular targets for innovative, minimally invasive diagnostic and therapeutic applications. Preliminary studies by our research group (preparatory to this proposal) have demonstrated the feasibility of utilizing immunoconjugates (in the form of immunoliposomes), incorporating monoclonal antibodies to EC activation antigens, to discriminate between normal and cytokine-activated human EC in culture and to "home" to the activated EC lining of the aorta associated with early atherosclerotic lesions, following intravenous injection in experimental animals.

To facilitate the translation of this technology to the clinical setting, the team initiated studies to develop robust, reproducible animal models of endothelial activation, in specific vascular geometries, and also to explore the use of radiolabeled immunoconjugates, directed to specific endothelial cell surface activation markers, for potential diagnostic and/or therapeutic applications, including (but not limited to) imaging of activated/dysfunctional endothelium in settings of tumor angiogenesis, early atherosclerosis, acute and chronic inflammation. During the past year, the team continued to pursue these thrusts, focusing both on the *in vivo* testing of adenoviral vectors, in a rodent model, to mediate a controlled high-level expression of endothelial activation antigen genes in defined vascular beds (Specific Aim 1), as well as attempting to adapt our immunotargeting approach to MRI imaging of activated human endothelial cells (Specific Aim 2). Exciting progress, in particular, has been made with the later aim.

Specific Aim 1: To develop a reproducible, robust small rodent model of endothelial activation that combines the use of adenoviral vectors (which can efficiently mediate high-level, localized expression of a given EC activation antigen, precisely where they are introduced into the vascular system), with a simple method of introduction into an anatomically defined vascular bed.

Progress: Work on this specific aim has continued to focus on refining our histochemical protocol for staining of rodent tissues for (adenoviral-mediated) LacZ expression, and on further pilot studies of the *in vivo* delivery of infective adenoviral constructs to mediate human E-selectin, and (control) LacZ, expression in defined vascular beds. Since the last report, fresh, high-titer stocks of viral vectors have been prepared, histochemical staining protocols have been standardized (with input from experts in the Morphology Core of the Vascular Research Division/BWH), and an additional 6 rats have been operated on using the modified protocol, described in the last progress report, for unilateral femoral artery infusion. All animals died within 5-8 hours after vector administration via the femoral artery; one other animal was injected intravenously, and survived. LacZ staining was positive in the liver of this animal. No LacZ staining was observed in any of the animals that died within 8 hours of arterial vector administration. The team is currently re-evaluating our surgical protocol, as it would appear that the vector preparation, per se,

was not lethally toxic (intravenous injected animal = OK), but that the combination of surgical stress in the femoral preparation may be contributing.

Specific Aim 2: To apply radiolabeling method(s) that result in high specific activity of labeling of Fab'2 fragments of EC activation antigen-specific monoclonal antibodies, and validate the retention of specificity and avidity of binding to a cultured activated EC monolayer that expresses the target antigen(s) of interest.

Progress: With MRI, the amount of paramagnetic label required for detection often far exceeds the number of binding sites. Previously, the team developed a number of different MR amplification systems. In the current pilot study, the team has directly imaged E-selectin expression in cultured HUVEC cells which have been activated by cytokine treatment *in vitro* (see Figure 1, below). The amplification is based on a Mab-peroxidase conjugate that condenses paramagnetic precursors of low relaxivity (tyraminyl-DOTA, R1 = 4 mMsec-1) to high relaxivity polymers (R1 = 14-20 mM second^{-1}). It should be noted that these determinations were made on suspensions of endothelial cells in a test tube geometry; further testing of this strategy of MR amplification will need to be applied to the surface of endothelial monolayers in petri dishes, thus better reproducing the *in vivo* geometry of the endothelial vascular lining. Nonetheless, these positive results are very encouraging.

2.2 Cancer Clinical Focus Area

Background and Significance

Cancer is the second leading cause of death in the United States. Early detection is almost always beneficial since the tumor burden is less, local therapy may be effective, and treatment is likely to be less morbid and less disfiguring. In many epithelial cancers there is a clear progression from normal tissue to a pre-malignant state: dysplasia occurs prior to the development of invasive carcinoma, providing an opportunity to prevent the development of even early stage cancers. While dysplastic epithelium may be difficult to distinguish from normal epithelium by gross appearance, several techniques offer promise to detect pre-malignant conditions allowing pre-emptive therapy to be instituted before cancer develops. We are currently developing such methods for cervical, esophageal, bladder, and colon cancer. Once cancer has developed, accurate staging is paramount in designing the appropriate treatment regimen. Failure to recognize small metastases may lead to the erroneous application of a local therapy to the primary tumor when in fact survival is determined by systemic disease. Conversely, the blind assumption of the presence of micrometastatic disease in patients with localized early tumors may lead to unnecessary and morbid adjuvant therapy regimens and discourage the application of potentially beneficial local treatment.

Just as early detection is a key element for improving outcomes in cancer treatment, so too are less invasive treatment modalities. Patients may fail to seek prompt medical attention when potential warning symptoms develop because they fear the pain and disfigurement associated with cancer treatment. In addition to encouraging cancer

patients to seek medical attention at an earlier stage, the application of minimally invasive therapies results in less trauma to the body with consequent preservation of immunocompetence, shown to be an important factor in eliminating microscopic foci of cancer. Heroic and extended surgical resections often do not improve survival or patient comfort compared with conventional treatment. Improved cancer care will result from earlier detection and precisely targeted therapy.

Task 1: MRI-guided Focused Ultrasound Treatment of Breast Cancer

The overall goal of this project is to develop a magnetic resonance imaging (MRI) guided focused ultrasound system for thermal coagulation of breast cancer. The first accomplishment for making clinical breast treatments practical is to develop and test phased array ultrasound applicators that allow the focal spot size to be increased. This is needed for two reasons: A large focal spot allows the tumors to be coagulated in a shorter time, making the treatment time practical. It also reduces the nonuniformities in the temperature field thus assuring better treatment response. The team has developed and tested a phased array applicator that is now implemented in a clinical MRI guided focused ultrasound system for breast cancer treatments. The team has also been able to test the ability of MRI-derived thermal dosimetry to determine tissue coagulation *in vivo*. These methods have now been implemented in the control of clinical MRI guided focused ultrasound in several institutions and are also being tested for use during MRI monitoring of thermal coagulation of tumors using laser fibers. Overall, the team has made significant progress that will make noninvasive MRI guided thermal coagulation of breast tumors practical for clinical testing.

Specific Aim 1: Develop treatment-plan procedures utilizing 3D-MRI information to determine the target volume and execute treatment. The team has developed and tested MRI compatible phased arrays to evaluate the effects of sonication time. The first goal was to evaluate the feasibility of inducing temperatures between 60 and 100°C in tissue volumes modeling breast cancer treatments during 10 – 60 second sonications.

Progress: Ultrasound phased arrays with sectored and concentric ring design were tested *in vivo* tissues to evaluate the sonication parameters that would produce large coagulated volumes. Most of the experiments have been with an eight-sector array that can only control the focal spot size. One hundred four element concentric ring transducers with sectors were also tested and found to provide control over the depth of the focal spot. The field produced by these transducers resulted in the coagulation of large tissue volumes with each sonication. Increased number of rings is expected to improve the depth control. The Food and Drug Administration has given a permission to use the sectored phased array (8-elements) for the clinical treatments. A further increase in the coagulated tissue volume was reached by increasing the sonications time with these phased arrays.

Specific Aim 2: Study the accuracy of MRI-derived temperature history for calculating the thermal exposure of tissue. The goal of this aim was to test and evaluate the feasibility of using MRI thermometry to estimate the temperature and thermal dose induced by the sonications and test its accuracy *in vivo* animal tissues.

Progress: A series of animal experiments were performed close to the threshold of the tissue coagulation. The temperatures during the sonications were mapped by using noninvasive MRI thermometry. The temperature histories were converted to thermal dose. Figure 1 plots the detected tissue coagulation as a function of the measured peak temperature, the thermal dose, and the applied acoustic power. The threshold is much sharper with the dose and temperature than with the applied acoustic power. This shows that the MRI thermometry can predict the tissue coagulation on-line at least in normal animal tissue. These methods will be used in clinical treatments to guide MRI guided ultrasound surgery in the future.

Specific Aim 3: Establish the thermal exposure required to assure complete tumor coagulation. This goal of this aim is to evaluate the feasibility of inducing tissue necrosis in a whole target volume by multiple sonications. The tissue effects will be studied using MRI imaging techniques and histology.

Progress: Multiple sonications with phased arrays were performed *in vivo* in rabbit tissues while mapping the temperature using MRI. Contrast enhanced MR images were used to evaluate the coagulated volume. Figure 3 shows an example a T1-weighted image of a volume sonicated in a rabbit thigh muscle *in vivo*. After the sonications and the MR imaging, the animals were sacrificed, and the tissue samples were obtained for histology evaluation (Figure 2). These experiments are ongoing.

Specific Aim 4: To test Specific Aim 3 in implanted rabbit tumors, in particular, to evaluate the influence of fat and tissue motion on the MRI dosimetry.

Progress: The team has evaluated the thermal maps obtained during *in vivo* sonications. Tissue voxels that contain both fat and other soft tissue do not show accurate temperature mapping. A double echo sequence with fat suppression has been tested and it was shown that these mixed voxel temperatures could be measured by using fat suppression. Fat suppression is now implemented in clinical breast cancer treatments. For pure fat, T1-weighted images may be adequate. A fast spectroscopic method was also tested for obtaining the fat and water peaks in each voxel. The temperature-insensitive lipid resonance was shown to provide an internal reference for the temperature-sensitive water resonant frequency shift. This method is also inherently more motion insensitive than standard techniques that use the water frequency alone.

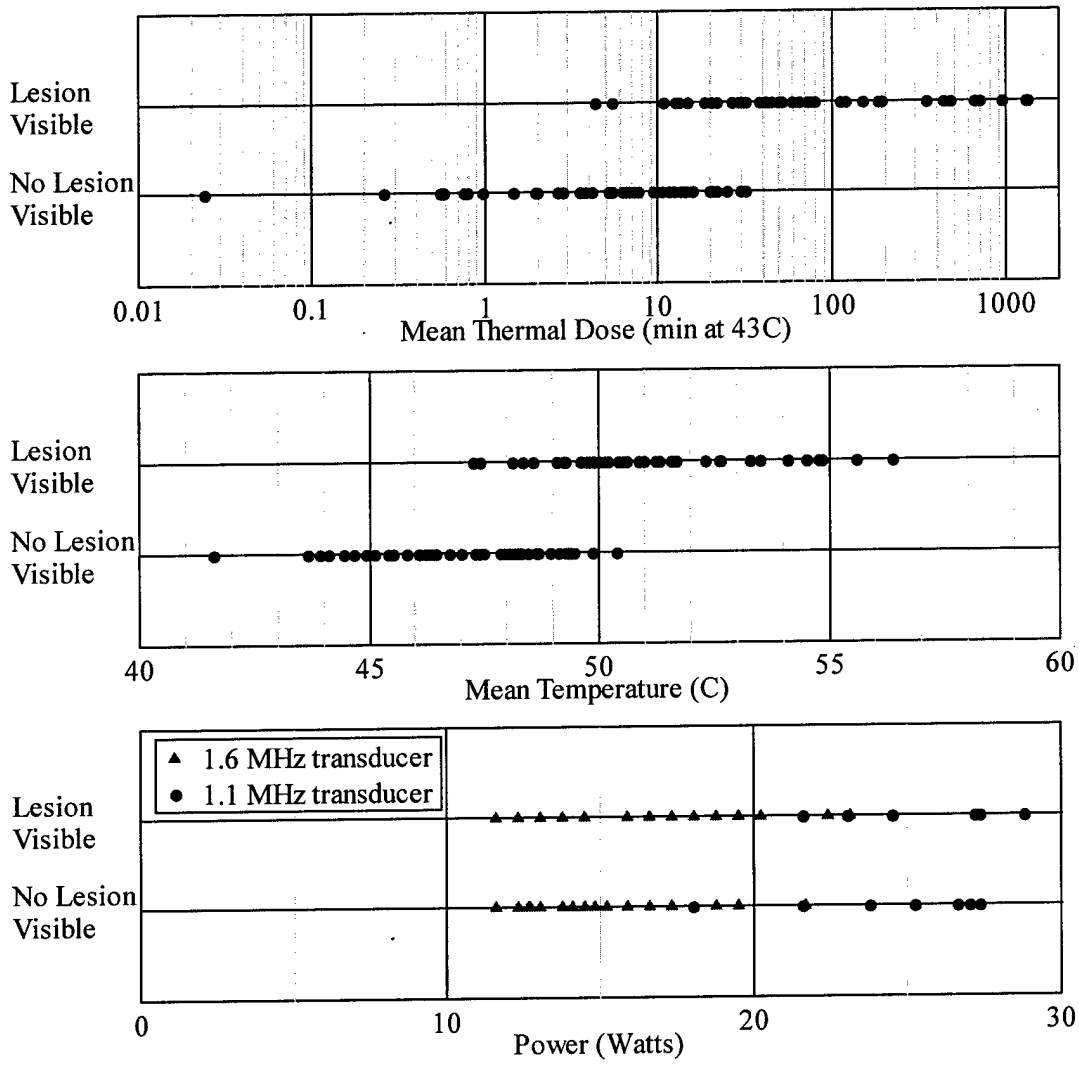
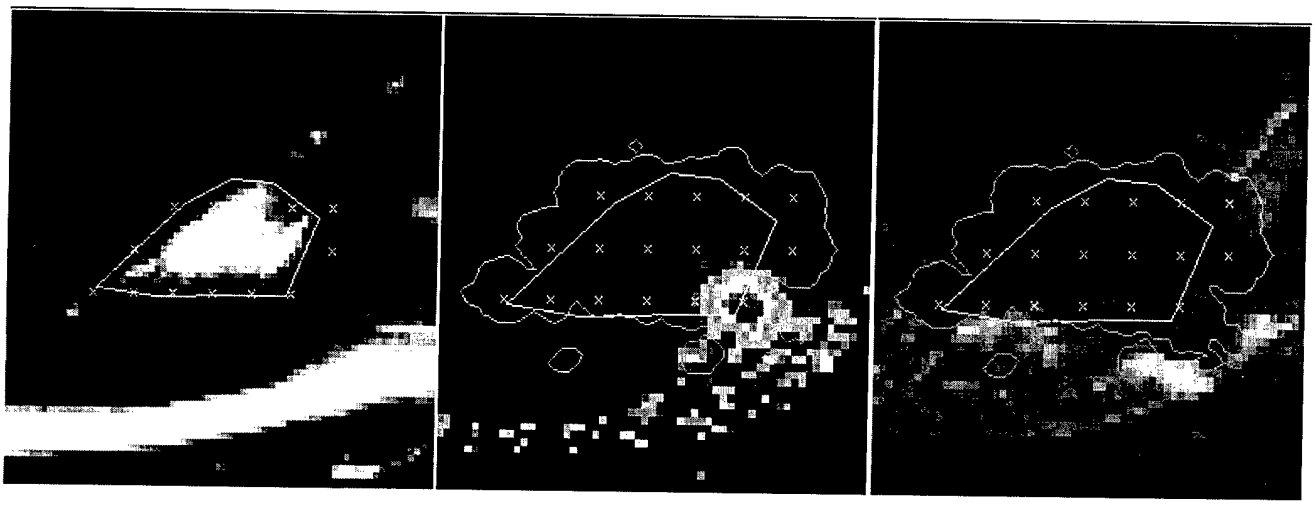


Figure 2. MRI guided focused ultrasound sonications of *in vivo* rabbit muscle tissue. Tissue coagulation as a function of MRI derived thermal dose, temperature and applied acoustic power.



A *B* *C*

Figure 3. Volume sonication by using focused ultrasound. (A) T2-eighted image with the target volume outline. (B) The temperature distribution measured during one of the sonications. (C) T1-weighted contrast enhanced image showing the lack of perfusion in the sonicated tumor. The Threshold thermal dose outline calculated based on the MRI derived temperature maps is also shown in the graph.

Task 2: Early Detection and Ablation of Epithelial Cancers

Specific Aim 1: Determine the accuracy of orally administered 5-animo levulinic acid (ALA) for marking dysplasia occurring in Barrett's esophagus.

Progress: To date 17 patients were enrolled in this trial. There were two study sites. The Massachusetts General Hospital was the primary study site and the Boston Veterans Administration Medical Center participates was a secondary study site. Eleven patients were studied at the Massachusetts General Hospital and six patients were studied at the Boston VA Medical Center. The mean peak PPIX fluorescence was significantly higher in Barrett's epithelium with high-grade dysplasia than in Barrett's epithelium without dysplasia. Thus, the preliminary results from this trial suggest that ALA-induced PPIX fluorescence appears to be a useful method of improving the detection of high-grade dysplasia in Barrett's esophagus.. The project was completed.

Specific Aim: Determine the clinical utility of Optical Computed Tomography (OCT) for imaging lesions in the GI tract. Perform a pilot trial of OCT in unselected patients undergoing upper endoscopy to assess the spatial resolution and clinical usability of the present system.

Progress: A total of 90 gastrointestinal subjects were studied with OCT. OCT image criteria for: 1) normal esophageal squamous mucosa, 2) Barrett's epithelium, 3) esophageal adenocarcinoma, and 4) gastric tissue, have been established which permit

accurate differentiation of these tissue types based on OCT images alone. The project was completed.

Task 3: Neuronal Injury and Neuroprotection in Epilepsy: Proton Beam Radiation for Intractable Epilepsy

A new model of proton beam radiosurgery (stereotactically focused irradiation) of the rat hippocampus has been developed. This model appears to be robust with brain necrosis evidenced reliably after a 3 month latency using doses of 90 Cobalt Gray Equivalents (CGE) or greater. This unilateral necrosis has been shown to correlate with increased T2 signal on MRI, decreased ability to perform the Morris Water Maze and the diminution of excitatory post-synaptic potentials and granule cell field spike obtained using *in vivo* microelectrode recordings. Positive alterations in heat shock protein, parvalbumin, calbindin and calmodulin have been detected. Upregulation of heat shock protein at non-necrotic doses may be important in explaining why low-dose irradiation reduces seizure activity in humans. These findings have been presented orally at the Congress of Neurological Surgeons Annual Meeting, September 2000, at the Spring Hippocampal Research Conference in spring 2000 and will be presented at the national Radiology Conference this fall.

Two additional time points after irradiation have been employed to further study the time course of irradiation effects on the rat brain. Twelve animals have been studied five hours after irradiation and eighteen animals ten months after irradiation. The animals studied at the five hour point show apoptotic cell death in the irradiated hippocampus in a dose-dependent fashion. The ten month animals appear to show physiologic changes even at the lower doses used; histologic analysis has not yet been done.

A cohort of 40 animals has been irradiated after receiving pilocarpine status epilepticus. These animals have been analyzed physiologically and their brains stained for histologic and immunochemical analysis. In addition to the immunochemistry previously used in the normal rat brain irradiation study, a "Timm Stain," that typically shows axonal sprouting after pilocarpine seizures, was employed to determine whether irradiation has any effect on this neuronal response to status epilepticus. Although preliminary results suggest that the pattern is altered with the higher doses employed, these results await formal analysis and neuropathologic review.

Specific Aim 1: To characterize the histologic and electrophysiologic effects of proton beam irradiation in the normal rat brain.

Progress: The MRI, physiologic, behavioral, and histologic effects of proton beam irradiation has been extensively studied in the rat brain (Figures 1 – 5). This study has incorporated over 70 rats and includes analysis at the hyperacute (5 hours), subacute (3 months) and chronic (10 months) time points. There have been several positive and negative findings which have been presented in the form of abstracts and presentations at national meetings and have been summarized above. These results form the basis for the manuscript "Proton Beam Radiosurgery Of The Rodent Hippocampus: MRI,

Neurophysiologic, Histologic, and Behavioral Findings," currently in preparation for submission.

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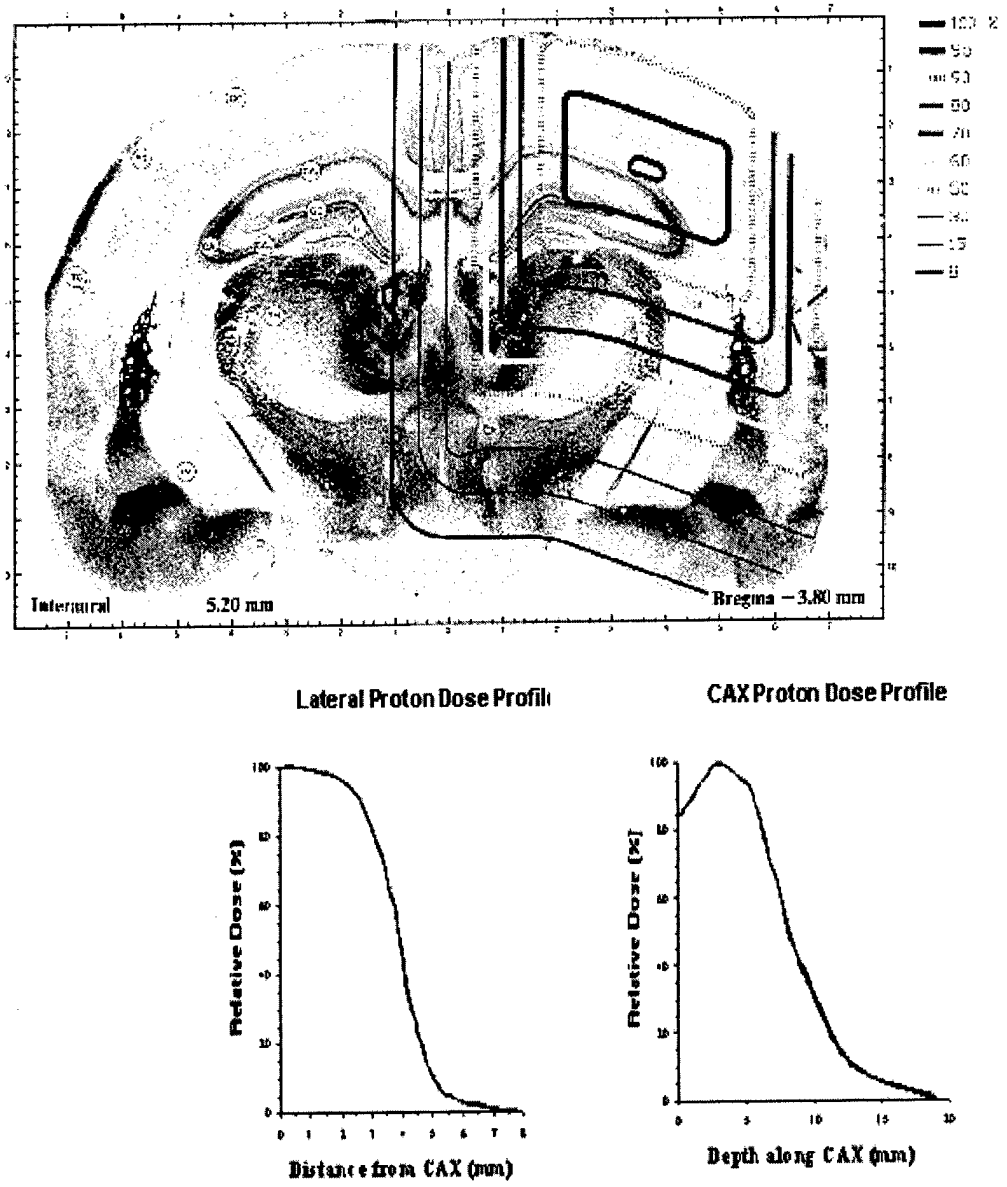


Figure 1. Proton Beam Dosimetry.

(a) (b)

Figure 2. Histology using Cresyl stain. a) 130 CGE (Cobalt Gray Equivalents): tissue loss, and b) 90 CGE: necrosis, edema, infiltration, cell loss, vascular dilatation.

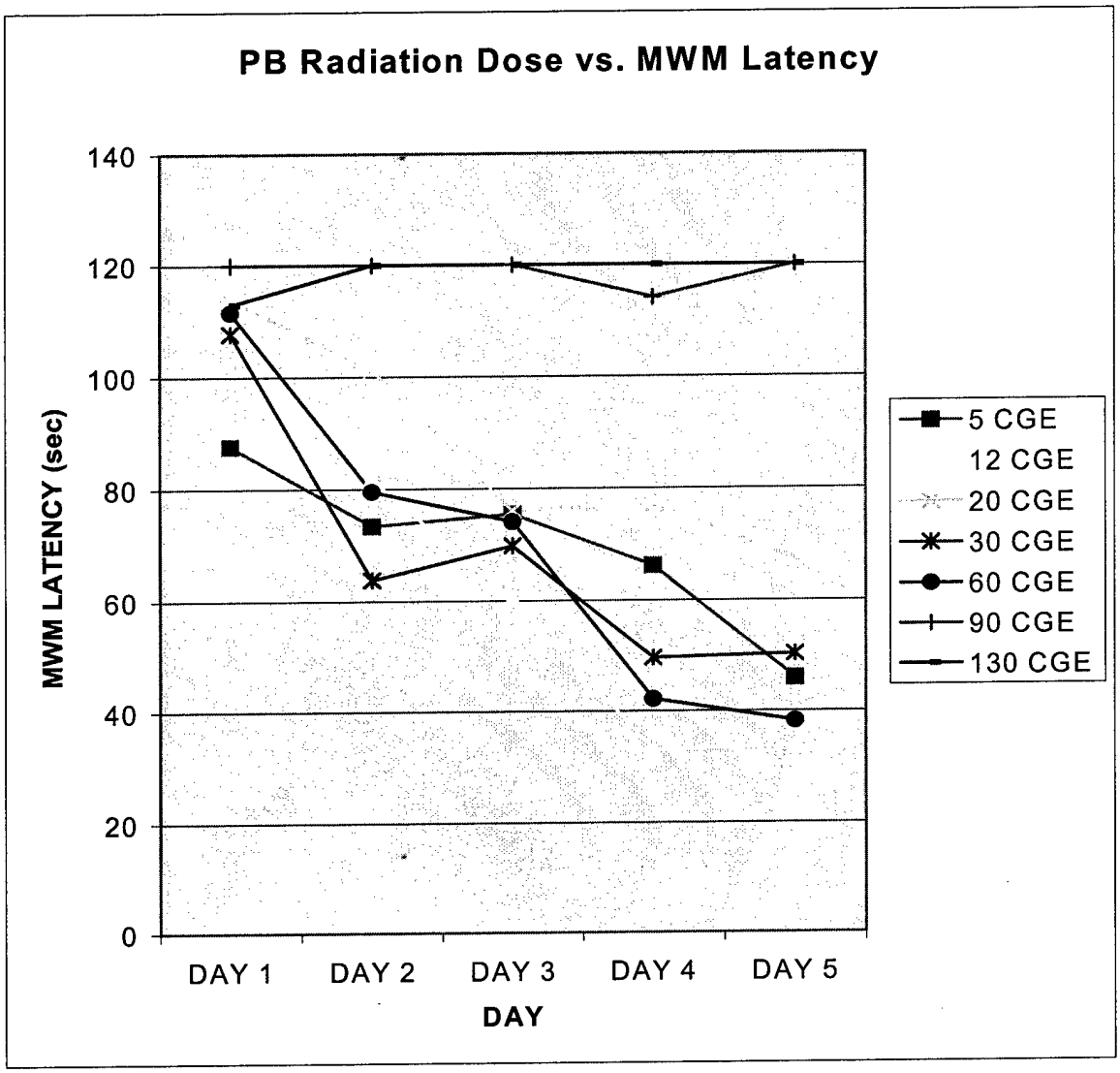


Figure 3. MWM Latency results with 5 to 130 CGE.

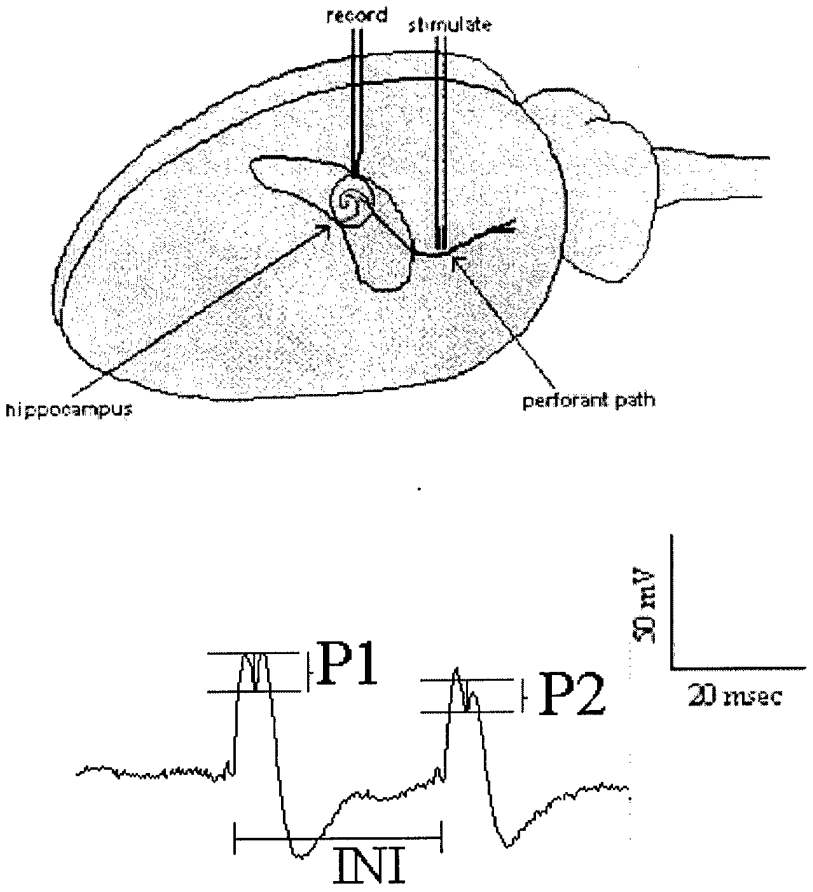


Figure 4. Microelectrode extracellular field potential recording from granule cells.

Specific Aim 2: To determine whether proton beam radiation can alter the neurophysiology or anatomic changes in animals that have undergone 24 hours of perforant pathway stimulation.

Progress: After finding in a pilot study that there was no alteration, a different seizure model (pilocarpine status) was employed. Forty animals that received pilocarpine status epilepticus were irradiated at varying doses of proton beam radiosurgery to determine whether this rendered an alteration in the physiology or histology/immunochemistry at the three month time point. The results are being collected and analyzed. Preliminary results show that physiology is not altered, but that sufficient doses of irradiation do disrupt the normal process of axonal sprouting typically seen after pilocarpine seizures and detectable using the "Timm Stain."

Specific Aim 3: To determine the brain MRI appearance of rodents subjected to varying dosages of proton beam irradiation as well as rodents that have undergone 24 hours of perforant pathway stimulation.

Progress: Results for MRIs performed on all animals in the subacute group (3 months) have been quantitated using computer-assisted volumetric analysis and basic statistics. These results are best appreciated in Figure 5. Essentially, the higher dose animals did show changes in T2-weighted imaging, restricted to the irradiated side. The animals at the chronic time point (10 months) have now been imaged with gadolinium-enhanced MRI and routine T2-weighted imaging. Positive gadolinium enhancement and T2 increased signal was seen for several animals and appeared to be dose dependent and included some lower dose animals, alterations not visualized at the three month time period. Statistical evaluation is currently underway on those computer-generated volumetric measurements. The project has been completed.

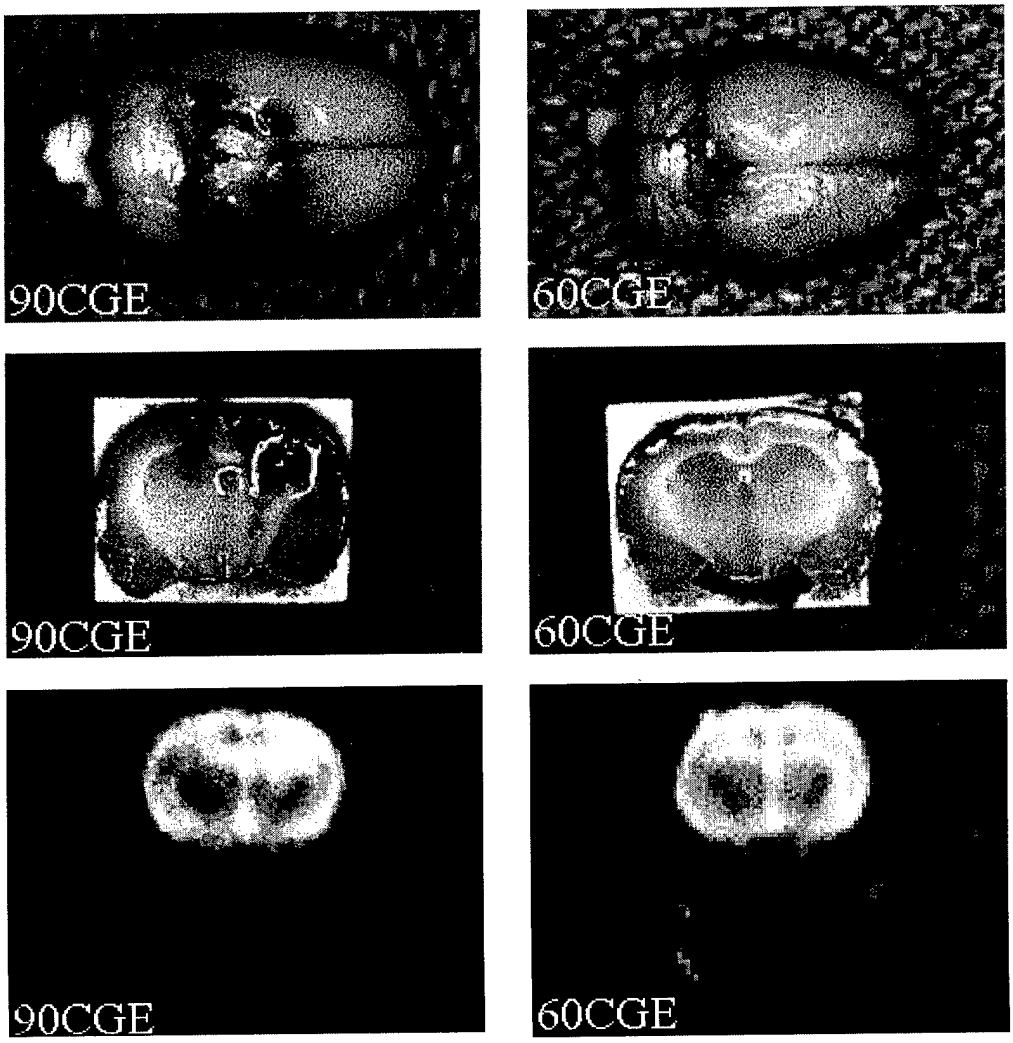


Figure 5. Gross brain: T2 MRI.

2.3 Stroke Clinical Focus Area

Stroke is the third leading cause of death and the leading cause of disability in the United States; over 700,000 cases occur annually. Most stroke is due to insufficient blood flow to brain tissue, so called ischemic stoke. Brain ischemia is also common to a number of other serious conditions including hypoxia, cardiac arrest, head trauma, drowning, circulatory arrest during cardiac or neurosurgery or vasospasm after subarachnoid hemorrhage. Stroke routinely robs a person of those higher order brain functions which underlie our very being.

Stroke due to brain ischemia or brain hemorrhage is now poised where "heart attack" was three decades ago, with many technologies offering promise to effect radical improvements in treatment. However, the time frame after stroke onset at which brain revascularization is successful remains short in comparison to the time window for coronary reperfusion, and the vasculature and tissue in the head are much less physically robust than the heart and coronary arteries. The CIMIT response to these challenges is a coordinated effort in diagnosis, therapy, and the integration of acute care, conducted by of a variety of specialists with unique expertise. The major long term goals of the CIMIT Stroke CFA are:

- To rapidly advance an internal bypass/therapy device to clinical trials. This device may extend by several hours the therapeutic time window for successful acute ischemic stroke therapy.
- To create a real time physiological state-of-the-brain imaging system. This system will be developed in a unique, specially designed neurointerventional suite which includes both state-of-the-art MRI and digital subtraction angiographic instruments at MGH.
- To develop diffuse optical tomography (DOT) technology to continuously monitor the brain for critical changes such as development of new ischemic tissue, hemorrhage, or reperfusion of previously ischemic tissue.
- To design and implement StrokeNet, a digital network for exchange of text, audio, video, and imaging data for diagnosis, treatment and long-term management of stroke and its associated conditions.
- To develop protocols that will greatly enhance the ability of treating physicians to predict stroke outcome at the time of the emergency evaluation.
- To develop a model for stroke costs (quality of life and financial) by which the usefulness of new technologies in stroke can be measured.

The CIMIT Stroke Program consists of four tasks,

- Assessment of outcome after ischemic stroke using combined clinical and Multi Detector Contrast CT scanning
- Image-Guided Endovascular Recanalization in Hyperacute Stroke
- Determination of Brain Perfusion and Brain Hemorrhage by Near Infrared (NIR) Spectroscopy in Stroke Patients
- ACCESS StrokeNet: Augmented Care in the Chain of Emergency Stroke Survival through the use of applied communications technology.

- Noise-Enhanced Tactile Sensation for the Management of Sensory Deficits in Patients with Stroke
-

Major Accomplishments

- Completed a demonstration of brain cooling (neuroprotection) to slow down the process of brain damage due to ischemia in an animal model system
- Developed a computer model which predicts the final infarction based upon the data from MR imaging studies performed on initial presentation to the emergency ward.
- Implemented perfusion imaging with CT in the acute care setting.
- Demonstrated Diffuse Optical Tomography for continuous monitoring of brain hemodynamics.
- Showed feasibility of energy assisted thrombolysis in an animal model system.
- Algorithm outcome assessment based on correlations of the initial clinical data and the CT perfusion study. Application of communications technology in the management of emergency stroke survival.

Task 1: Acute Stroke Management – Neuro-Protection

Specific Aim 1: Develop a means to quickly cool the brain cortex to afford neuroprotection.

Progress: The bioheat transfer problem of cortical surface brain cooling was modeled using a one-dimensional steady state equation as described by Pennes (original work done in 1948). Initial parameters for the model were estimated based on anticipated values for brain tissue temperatures during surface cooling. A cooling pad was developed to induce regional cerebral hypothermia on the cortical surface of the dog. When studies of cortical brain cooling *in vivo* were completed, additional empirical data became available and were fed into the bioheat transfer equation to obtain a more accurate model. Results from this refined model were then compared with measurements from *in vivo* depth mapping. The project was completed.

Task 2: MRI Guided Rapid Laser Endovascular Photoacoustic Recanalization (LEPAR) for Hyperacute Stroke and Stroke Predictive Modeling

Specific Aim 1: Develop a new model using non-human primates to define irreversible brain injury by diffusion MRI.

Progress: The team has perfected a novel and extremely powerful model for defining irreversible primate brain injury by diffusion MRI. In the course of perfecting this model the team has developed an internal bypass methodology that is likely to be beneficial to patients suffering from large vessel stroke. Our novel endovascular approach produces highly reproducible infarcts. The infarcts are located in a location in the brain where survival studies are now possible. In perfecting the model the team also developed an internal bypass method which permits us to fully control the duration of ischemia with a precision that has never been obtained in nonhuman primate studies of stroke. This

methodology will now be employed to systematically define irreversible brain injury by diffusion MRI. Our demonstration of the capability of this bypass approach to keep brain viable despite arterial occlusion also raises the possibility of using this approach in humans. This is an exciting new approach to minimize injury in patients with major stroke syndromes.

Specific Aim 2: To demonstrate efficacy and tissue safety of the LEPAR device and to maximize patient safety by defining the irreversible brain injury probability by diffusion MRI in a primate model.

Progress: To date the team has studied 7 animals. Placement of the catheter for remote occlusion of the middle cerebral artery was performed under X-Ray fluoroscopic guidance and a perfusion deficit in the appropriate cerebral territory was verified by angiography. Of these 7 animals, 2 received CT scanning only, 2 received CT and MRI, and 3 received MRI scanning only. Occlusion durations between 2 and 3 hours were used. MRI scans included anatomical T1 and T2 weighted images, dynamic contrast enhanced perfusion weighted images (PWI) and diffusion weighted images (DWI) which define infarct extent at very early time points. MRI image analysis was carried out offline on Sun/Solaris and LINUX workstations. Images of hemodynamic parameters (relative blood flow, volume and mean transit time: rCBF, rCBV, rMTT) and apparent diffusion coefficient (ADC) were generated to define the extent of tissue injury, and for comparison with histological staining. On animals demonstrating acute focal abnormalities on MRI (T2, DWI or PWI) the initial lesion volumes were: 1.3ml (7/99), 1.6ml (4/00), 2.1ml (8/00), 0.9ml (9/00). Thus the mean lesion volume created by the interventional procedure was 1.47±0.50ml, demonstrating good reproducibility in lesion creation with this approach.

To start with, animals were occluded for a fixed duration by insertion of the microcatheter into the middle cerebral artery, with reperfusion effected by simply withdrawing the catheter. MRI images were typically acquired during the occlusion period and also during reperfusion. An example of serial MRI data from such an experiment is shown in Figure 1. The animal was scanned during reperfusion and in this case, the team was able to perform a comparison with post-mortem stained brain slices. This animal was imaged from 30 minutes after reperfusion, to 4 hours after reperfusion. In this animal, reperfusion was incomplete and a small region of reduced CBF and elevated mean transit time (MTT) persisted throughout the scans. Figure 1 show serial images from one slice in this animal covering the reperfusion period. The fast spin-echo T2 weighted images show focal hyperintensity that persists throughout the 4 hours of reperfusion. The total lesion volume measured from the T2-weighted scans decreased slightly from 1.3ml to 1.2ml over this time. The post-contrast T1-weighted images show progressive hyperintensity in the lesion area, indicating blood brain barrier disturbance. The DWI images show hyperintensity matching the T2-weighted changes, which became somewhat more pronounced during reperfusion. ADC values however were heterogeneous in the lesion area, with some areas of depressed and some areas of elevated diffusion, which persisted throughout reperfusion. As a result, the lesion is difficult to see on the ADC images. The CBF maps also show a matching perfusion deficit which is slightly smaller than the DWI abnormality. The imaging abnormality

compared well in terms of anatomical location with the infarct areas defined by postmortem TTC staining.

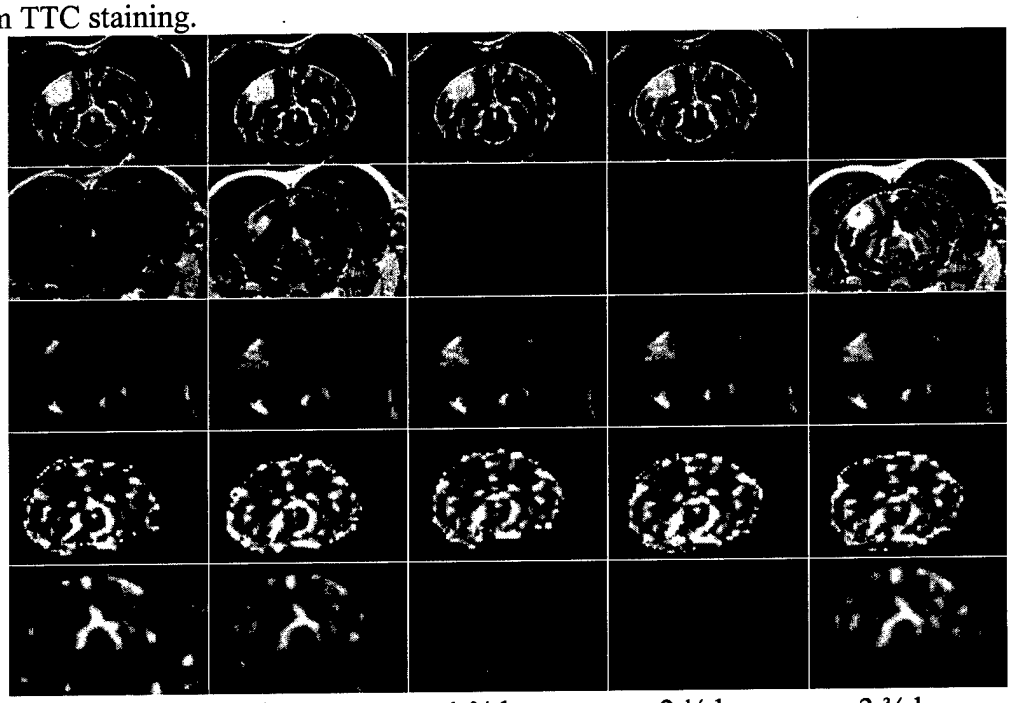


Figure 1. MR images of a single slice for one macaque during 4 hours of reperfusion following 3 hours of MCAO (middle cerebral artery occlusion). The horizontal axis is the approximate time of each image set after reperfusion.

Because the ischemic lesion is created under fluoroscopic guidance, the occluding catheter is placed in the fluoroscopy suite. Some time elapses (15 to 20 minutes) due to transportation of the animal to the MRI suite before the first MRI images are acquired. Ischemia is maintained during transportation. The consequence of this transport requirement is that the team can not acquire MRI images before occlusion, or during the earliest times after occlusion. To overcome this limitation, the team has expanded the model to include arterial bypass. In the bypass model, arterial blood from the femoral artery catheter is pumped through the occluding microcatheter immediately after it is placed in the MCA. The pump rate is calculated to provide sufficient blood flow to keep the tissue alive for the typical lesion sizes created by this approach. By keeping the bypass pump running during transport of the animal to the MRI scanner, tissue in the lesion area is maintained viable until baseline MRI scans have been obtained. The pump is then switched off (or switched to pure saline infusion) to create a focal stroke for a well defined period (1 to 3 hours).

Images from the first animal using this updated model are shown in Figure 2. These were acquired 90 minutes after MCA occlusion. Blood was pumped up the microcatheter at a rate of about 1ml/min. The lesion size obtained in this animal corresponded at a perfusion rate of about 50ml/100g/min, which was sufficient to maintain viability of brain tissue. Lack of significant injury, as illustrated by the normal looking T2, diffusion and ADC images (in contrast to Figure 1) shows that the bypass circuit was indeed able to prevent

ischemic injury to the tissue for 90 minutes. This is an important advance for this study because it provides a means to create well defined periods of focal cerebral ischemia within the MRI magnet allowing the team to follow all stages of stroke onset.

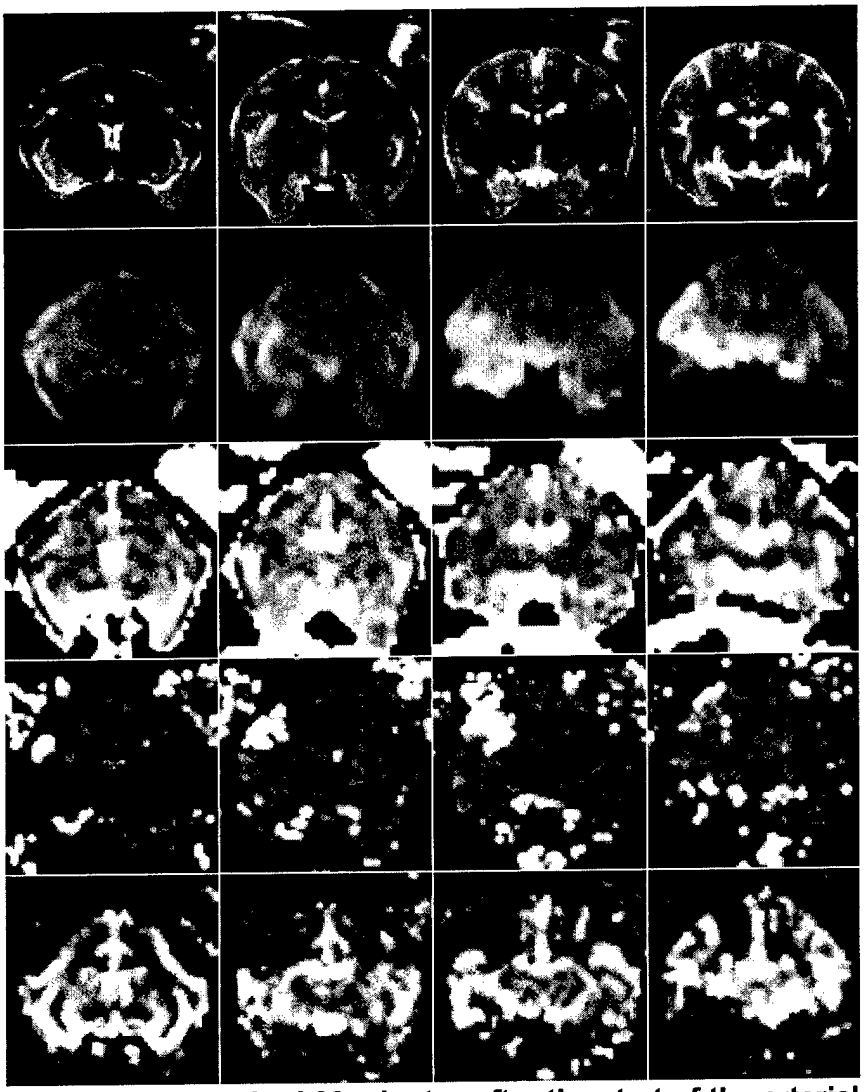


Figure 2: Multislice images acquired 90 minutes after the start of the arterial bypass. In spite of a clear perfusion deficit (lower 2 rows) due to the occluding microcatheter, there is little or no evidence of injury (upper rows) due to the blood supplied by the bypass.

Task 3: Optical Monitoring and Imaging of Stroke

The second year aims for the project "Diffuse Optical Tomography of Stroke" focused on continued development of (1) instrumentation and (2) algorithms, and testing in (3) animal and (4) human studies. To date, prototype construction of the 3rd generation CW imaging system and 1st generation RF system has been completed, and initial progress has been made in applying the model-based calibration ideas to image reconstruction.

Specific Aim 1: Finish the construction and testing of the 3rd generation CW instrument and the 1st generation RF instrument. Develop DSP (digital signal processing) technology in hardware to enable faster image acquisition with more detectors. Implement more wavelengths into the imaging systems to enable sensitivity to metabolic indicators as well as hemodynamic signals (move from 2 to 4 wavelengths).

Progress: A photograph of the 3rd generation CW imaging system is shown in the Figure below. The system has 18 sources that are frequency encoded such that the 16 detectors can discriminate the signal from each individual source. The system specification allows images to be acquired at 20 Hz or slower depending on the strength of the optical signal. Isolation of the individual channels is better than 80 dB.

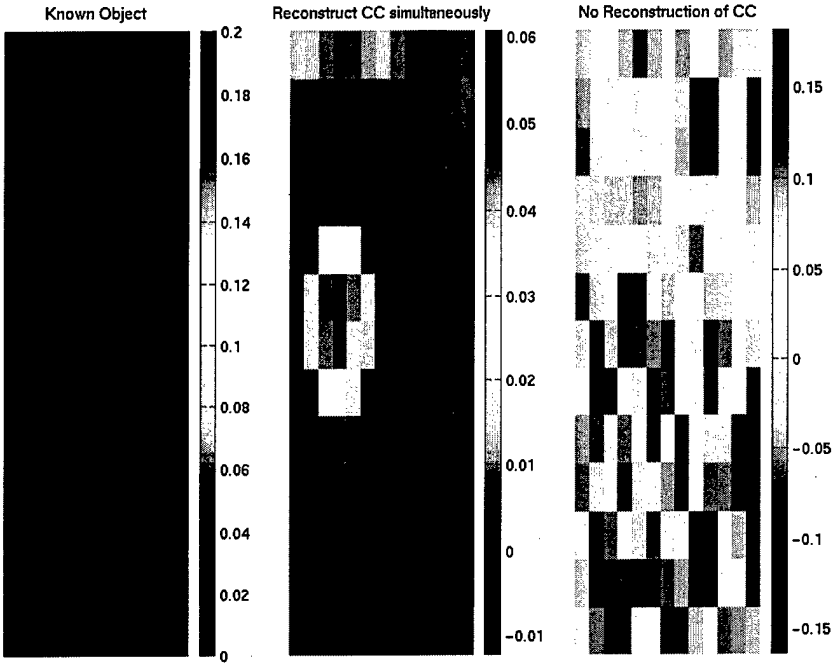
The 1st generation RF imaging system has been completed. Its performance specifications are presently being measured.

Specific Aim 2: Develop quantitative 3D reconstruction algorithms. The endpoint of this aim is to develop quantitative 3D reconstruction algorithms. This is a challenging endpoint requiring multiple parallel investigations. The project will continue the investigation of constrained image reconstructions to exploit prior information to reduce the number of unknowns in the inverse problem. The investigators will work to better understand the effects of the layered structure of the head and then correspondingly optimize the reconstruction algorithms. They will implement newly published Bayesian and clustering techniques to further reduce the number of reconstruction unknowns to obtain 3D images.

Progress: When the source and detector fiber optics are attached to the scalp, there is a coupling factor which reduces the light amplitude by an unknown factor. This cannot be pre-calibrated as it depends on the pigmentation of the skin, orientation of the fiber, and the amount of hair residing between the fiber and scalp. Furthermore, this coupling factor is very sensitive to the position of the fiber and will change with each placement. The investigators are therefore working on a model-based method for calibrating these coupling coefficients from data collected with the fibers placed on the scalp.

Previously, the team had made progress towards achieving coupling coefficients by assuming that the tissue has spatially uniform optical properties. That is, the spatially varying contribution of the scalp, skull, cerebral spinal fluid, gray and white matter, as well as any hemorrhage or infarcted tissues was ignored. The team also modified the previously defined approach to deal with spatially varying optical properties. The latter was accomplished by treating the coupling coefficients as unknowns in the same way that spatially varying optical properties were treated as unknowns. The team created a linear

model that relates measurements to unknown optical properties within each volume element in the medium and to unknown coupling coefficients. Thus, calibration and imaging is achieved simultaneously through optimization of a linear problem. An example of the power of this technique is shown below where a known object is compared to reconstructed images with and without simultaneous calibration. Without calibration, the image essentially reveals the position of sources and detectors by reconstructed increased or decreased absorption to compensate for the unknown coupling of the fiber optics.



Specific Aim 3: To cross-validate the sensitivity and quantitative accuracy of the optical measurements with structural and functional information obtained with MRI, and to obtain preliminary results for "spin-off" projects. The objective of this aim is to cross-validate the sensitivity and quantitative accuracy of the optical measurements with structural and functional information obtained with MRI. A secondary objective is to obtain preliminary results for "spin-off" projects for which funded will be sought from NIH. The piglet cerebral hemorrhage studies that were initiated in the first year will be completed. A study of focal ischemia in a rat model will also be started. This dual approach for ischemic stroke is being implemented to provide an easy, well controlled model for validation afforded by the rat, and to have a model closer in anatomy and size to a human. Measurements will be made with a third series of images with Dr. Gonzalez using his macaque ischemic stroke model.

Progress: No activity, pending further development of the DOT system

Specific Aim 4: To demonstrate the clinical utility of DOT for continuous monitoring and diagnosis of cerebral hemorrhage and stroke. The endpoint of this project is to demonstrate the clinical utility of DOT for continuous monitoring and diagnosis of

cerebral hemorrhage and stroke. A pilot study will be started in patients to determine the sensitivity to these pathologies and to identify practical problems associated with transferring the DOT technology from "the bench to the bedside".

Progress: Pending review of the Human study proposal (#98-09154) to be reviewed by the DoD HSRRB in November 2000.

Task 4. ACCESS StrokeNet: Augmented Care in the Chain of Emergency Stroke Survival through the use of applied communications technology.

This project was supported by non-DoD funds

Task 5: Noise-Enhanced Tactile Sensation for the Management of Sensory Deficits in Patients with Stroke

Specific Aims: Design and construct a suitable apparatus for patient experiments. Demonstrate the feasibility of both the apparatus and an experimental protocol through implementation in-patients with stroke; collect data on patients with stroke. Analyze data to test the hypothesis that electrical noise can enhance the ability of patients with stroke to detect subthreshold mechanical stimuli.

Progress: This project has been on hold since June 1999. Notification from the HSRRB of the Department of Defense, enabling the project to proceed was received in October 2000.

2.4 Trauma and Critical Care CFA

Background and Significance

The aggressive application of definitive therapeutic and diagnostic technologies is integral to the management of critically injured civilian and military patients. Often these injuries occur in situations where the assets of a traditional medical facility are not available. This is particularly true on the battlefield, where casualty management depends on an early and accurate assessment of the injury coupled with the delivery of a minimal set of therapeutic options designed to stabilize the patient prior to and during transport. The U.S. military Joint Chiefs of Staff recognize the future dependence of medic performance on the application of advanced technologies to meet these requirements. New doctrine stressed in the Joint Vision 2010 statement and the J4 Medical Readiness Conference on *Forward Resuscitative Surgery* identifies the need for the development of non-invasive techniques, devices and treatment adjuncts that provide a new level of care, quickly following trauma, to assist the medic in the management of battle trauma.

In civilian trauma and critical care, similar challenges exist along the entire continuum of health care delivery from the first minutes after trauma or medical catastrophe, throughout the hospital treatment, recovery and rehabilitation phases. Significant shortcomings in our ability to accurately diagnose and manage CNS injury and stroke in

the pre-hospital phase may contribute to poor outcomes in some patients. These shortcomings also severely limit the lifesaving application of early, advanced treatments, which depend on an accurate non-invasive assessment of intracranial hemorrhage, pressure and regional blood flow. New techniques and strategies designed to intelligently assess the course of recovery following trauma to detect regional ischemia, immune dysfunction and assist in the management of shock could significantly improve the outcomes of these patients.

CIMIT provides a rich and particularly unique foundation to develop new techniques to not only improve survival and outcome from acute trauma and injury but also improve management and rehabilitation. Broad clinical talents have been identified to participate in CIMIT that deliver a spectrum of trauma, critical care and rehabilitation care and will provide the basis for design, testing and application of new technologies to meet these challenges. This clinical focus group, working closely with the Advanced Technology teams, is designed to aggressively develop an initial set of technologies that ultimately could affect a broad spectrum of our nation's population, including the active duty military population during peacetime and war.

General Description

The Trauma and Critical Care CFA at CIMIT is closely integrated. The fields currently investigated cover the spectrum of medical care for the injured. Dr. Ling's RAFTS studies are based on pre-hospital Care. Dr. Puyana's studies focus on resuscitation and ICU care, which are the immediate steps following prompt diagnosis and initial attention in the battlefield. The Draper Laboratory group is now exploring the frontier of advanced laboratory diagnostics in cytokine and microbiological detection as an ATT that will have enormous implications as point of care assays either at the far forward hospitals or at major tertiary and quaternary medical centers. The CFA directly addresses the challenges of treating military casualties, as well as providing significant potential benefits to civilian health care. Tasks include:

RAFTS - A Fieldable Device to Support Triage Decisions The long term goal is to develop a practical, lightweight, portable and robust tool for use in the extreme far forward environment by combat medics to diagnose common pathologic conditions sustained in combat. This device will provide unambiguous data (red light/green light) indicating that a pathologic condition exists. This information can then be used to direct proper triage/evacuation and, possibly, initiation of appropriate therapy. Over the next year, the objective of this study is to determine whether application of a small lightweight and inexpensive device based on radiofrequency (RF) signals can noninvasively and accurately detect the presence of pneumothorax and compartment syndrome. The device is given the acronym RAFTS, which stands for radio frequency triage system

Assessing the Severity of Hemorrhagic Shock It is recognized that preventing death from hemorrhagic shock, and the limitations of therapeutic methods, are important areas in which new technology could be of benefit for the wounded soldier. A platform has been developed for minimally invasive monitoring of cellular dysfunction during and after hemorrhage. Death after severe injuries in

military conflicts or civilian trauma continues to result from massive blood loss or the late consequences of incomplete cellular resuscitation, Multiple Organ Dysfunction Syndrome, (MODS). This CIMIT sponsored research can significantly decrease combat casualty and civilian mortality as well as reduce the cost of health care of trauma victims.

Task 1: Application of Microwave Imaging to Rapid Non-Invasive Detection of Intracranial Hematoma

To begin, the device being developed in this project (Hematoma Detection System, HDS), has been renamed to "radio frequency (RF) triage system (RAFTS)." Work on RAFTS has continued and the team has focused their efforts on initiating human clinical trials.

In this past year, the team successfully completed the application of RAFTS to diagnosis of intracranial hematomas using *in vitro* testing of cadaveric pig brains. Results from this work demonstrated that RAFTS can differentiate hematomas from brain and skull. Subsequently, the team reported completion of *in vivo* studies performed on live anesthetized pigs. These studies showed that the RAFTS could accurately detect the presence of hematomas at epidural, intraventricular, subdural and intraparenchymal sites in a clinically relevant model.

Recently, preparation has begun for human clinical studies. A clinical use proposal has been submitted to the USUHS human use institutional review board (IRB) and the U.S. Army IRB. Preliminary reviews by both have been favorable. The USUHS full approval is anticipated. Army IRB approval will be sought next.

Additionally, preparations have been made to continue the *in vivo* studies of pneumothorax and compartment syndrome in pigs. It is anticipated that this aspect of the proposed work will be completed within the coming fiscal year.

Specific Aim 1: To demonstrate the feasibility of applying the microwave diagnostic tool to identify pneumothorax.. In particular, to demonstrate the feasibility of applying the microwave diagnostic tool to identify the presence of blood in the epidural space.

Progress: Pilot studies were initiated exploring the potential of applying the hematoma detector system to diagnose other pathologic states associated with combat casualties. Two conditions in particular are pneumothorax and compartment syndrome. Both are occult disorders that may be missed by the expedient physical examination a wounded soldier receives on the battlefield.

Measurements were made in 2 pigs. One received a 100cc pneumothorax (PTX) and the other, a compartment syndrome from 2cc of blood.

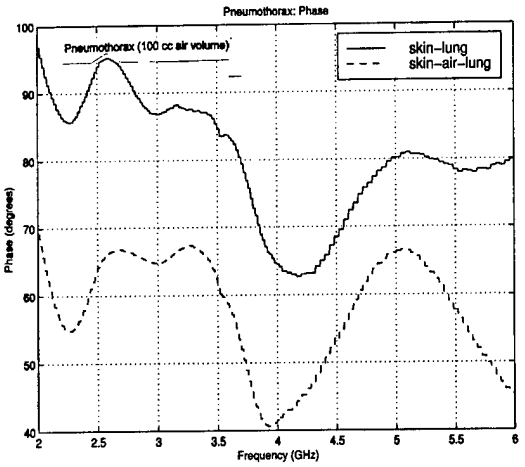


Figure 1. PTX phase vs. frequency at 100cc freq 100 cc

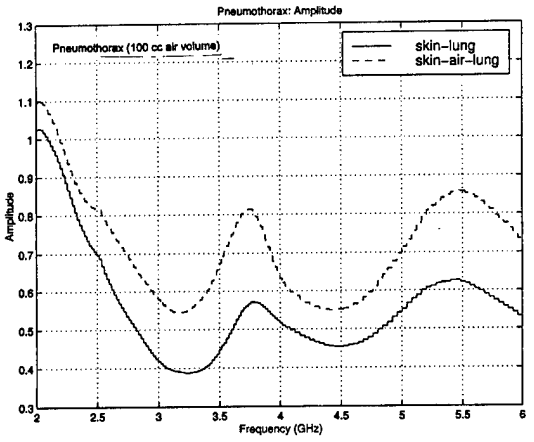


Fig. 2. PTX amplitude vs.

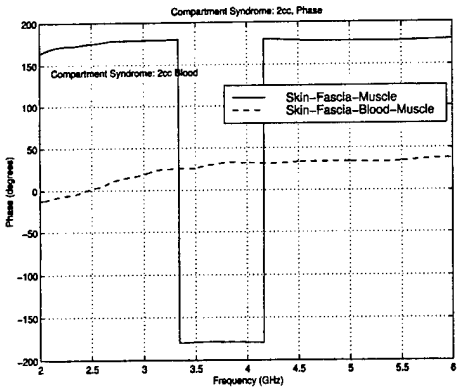


Figure 3. Compartment Syndrome, 2cc.

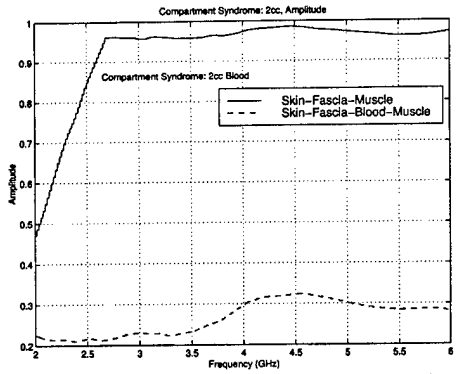


Fig. Compartment Syndrome, 2cc.

Figures 1 and 2 present the signature of the skin, thorax, and lung interfaces. Figures 3 and 4 present the signature of the skin, fascia, and muscle interfaces. Data are presented as amplitude and phase versus frequency.

There are clear discernible differences between the signatures, indicating the effect of the presence of the air or blood on the reflected signal. It appears that obtaining the real parts of the back scattered signal will be the most effective way of detecting the presence of air in the thorax or blood beneath the fascia. It is this effect that presents an opportunity to detect the presence or absence of pneumothorax and compartment syndrome from blood. Employment of standard neural net algorithms will enhance the detection probability and reduce the human interface in the system.

Specific Aim 2: Demonstrate the feasibility of applying the microwave diagnostic tool to identify compartment syndrome, including:

- Demonstration of the feasibility of applying the microwave diagnostic tool to identify the presence of blood in the lateral cerebral ventricles.
- Demonstration of the feasibility of applying the microwave diagnostic tool to detect

intraventricular hematoma.

Progress: Male Yorkshire pigs weighing from 25-50 kg were used in these studies. There were 5 pigs subjected to each test volume. Each pig was premedicated with ketamine and xylazine, I.M. Following, pentobarbital, I.V., was used as an anesthetic. A catheter was placed surgically through a burr hole into the epidural space. Interrogation using the microwave HDS was performed prior to introduction of blood so that each animal could serve as its own control. Subsequently, either 2cc, 5cc or 10cc of autologous blood was administered via the catheter into the epidural space. Shortly after treatment, each pig was again interrogated using the microwave HDS. The HDS antenna was held 6 cm away from the pig's head.

Raw data was collected using a network analyzer. Data was processed using the MUSIC algorithm and the MATLAB computer program. The data was displayed as amplitude or phase as a function of radio frequency. Both real and imaginary data were used. Investigators analyzing the raw data were blinded to the treatment.

Each signature profile is composed of measurements made at each of 400 equally spaced frequencies between 2 – 6 GHz. Profiles were integrated. Resulting data for the baseline signature was compared to the injury signature at the same frequency point using paired analysis (paired t-test). A level of $p \leq 0.05$ was predetermined to be significant.

Due to a change in institutional policy, CT scans could not be obtained in pigs. Therefore, post-mortem analysis was performed to verify hematoma location.

Following administration of epidural blood, there is a shift in both amplitude and phase from control (Figures 5 and 6, respectively). There was also a change in signature from baseline for amplitude. Although there was a shift noted at 2cc, it was not found to be significantly different from control.

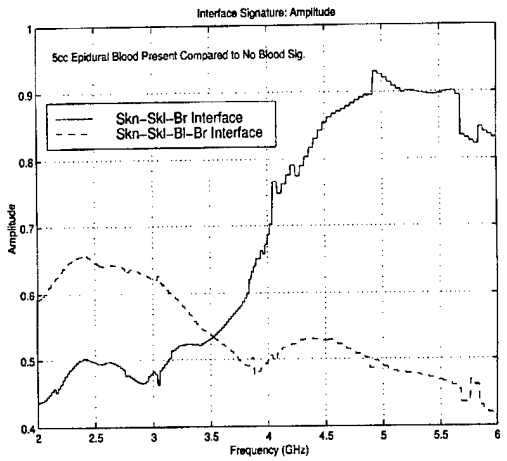


Figure 5. Epidural hematoma, 5cc

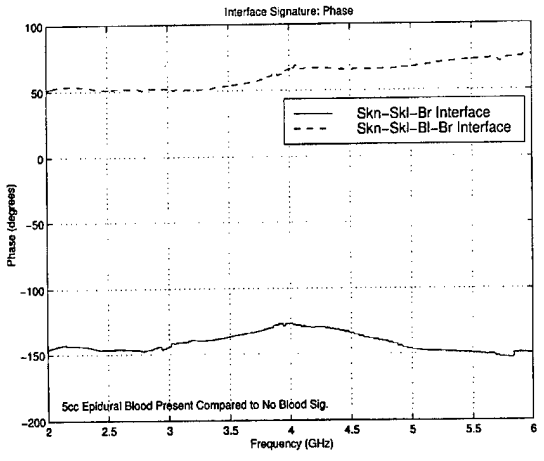
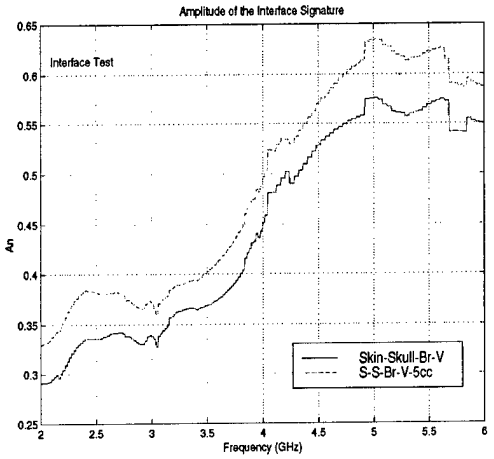


Figure 6. Epidural hematoma, 5cc

The baseline signature for both amplitude and phase was different for each pig. This appeared to be related to differences in surface contours of each pig's head as well as the individual size. Unfortunately, this finding prevented the determination of a single characteristic baseline signature that was representative of all pigs. Thus, comparisons of normal versus epidural injured states had to be done with each pig serving as its own control.

Intraventricular Hematoma:
The Methods were similar to those summarized above in Specific Aim 1.

Following administration of intraventricular blood, there is a shift in both amplitude and phase from control. The shift is significant at 5cc and 10cc volumes (Figures 7 and 8). Although there was a shift noted at 2cc, it was not found to be significantly different from control.



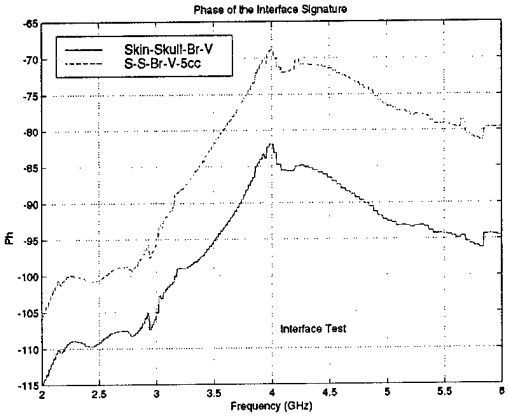


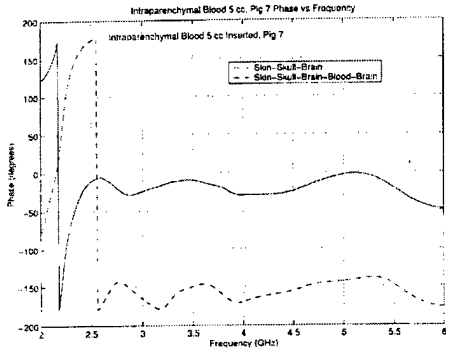
Figure 7. Intraventricular hematoma, 5cc

Figure 8. Intraventricular hematoma, 5cc

The baseline signature for both amplitude and phase was different for each pig. This appeared to be related to differences in surface contours of each pig's head as well as the individual size. Unfortunately, this finding prevented the determination of a single characteristic baseline signature that was representative of all pigs. Thus, comparisons of normal versus intraventricular hematoma injured states had to be done with each pig serving as its own control.

Intraparenchymal Hematoma:
The Methods were similar to those summarized below in Specific Aim 1.

Following administration of intraparenchymal blood, a significant shift in RF signature from baseline could not be detected. This was true for all volumes tested, including 10cc. At 10cc, there was a shift in amplitude from control at a narrow frequency range, 4.6 to 4.7 GHz. It is only apparent at 5 and 10cc volumes (Figure 9).



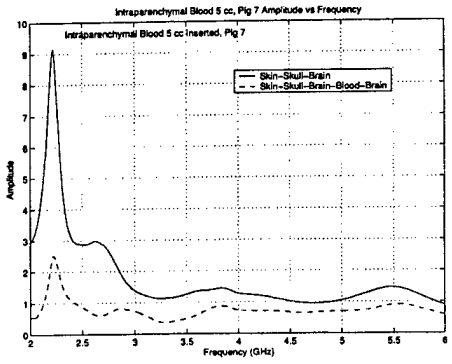


Figure 9 and 10. Intraparenchymal phase vs freq 5 cc.
The baseline signature for both amplitude and phase was different for each pig. This appeared to be related to differences in surface contours of each pig's head as well as the individual size. Unfortunately, this finding prevented the determination of a single characteristic baseline signature that was representative of all pigs. Thus, comparisons of normal versus intraparenchymal hematoma injured states had to be done with each pig serving as its own control.

Further Work: Human use institutional review board (IRB) approval for a clinical study using the RAFTS to be conducted at USUHS has been submitted to both USUHS and Department of Defense. The initial evaluation of the proposed study to examine the head, chest and leg of 15 normal human volunteers has been submitted. The purpose of this study will be to obtain baseline values. The hypothesis is that there are no significant differences in the RAFTS signature for head (or chest or leg) among normal humans. If this proves to be true, then clinical trial in trauma patients can be prepared. If this proves to be false, then modifications of the trauma clinical trial will be needed, such as side-to-side comparison.

USUHS IRB initial evaluation has been favorable. Minor modifications to the consent form were requested and have been completed. Final approval is expected at the next IRB meeting enabling the study will begin.

The team also had a meeting with the Food and Drug Administration (FDA), Small Devices Radiologic Group. It was concluded that RAFTS did not need an Investigation New Device Exemption to proceed to clinical trial.

Task 2: Near-Infrared Reflectance Spectroscopy (NIRS) to Assess Regional Ischemia both during Trauma Resuscitation and at the Bedside in the Intensive Care Unit

The overall objective of this research effort is to use NIRS and other new minimally

invasive technology to determine the severity and reversibility of hemorrhagic shock by means of assessing organ specific cellular function and metabolism.

Background: The application of NIRS for the assessment of liver dysfunction during hemorrhagic shock has been described. Initial observations included the confirmation of previous experiments corroborating the use of our NIR probe for the non-invasive assessment of hepatic acidosis. Furthermore, by studying oxygen extraction from the liver, it was shown that hepatic acidosis is a more reliable end point of resuscitation in shock than tissue oxygenation. In a second set of animal experiments, it was shown that the use of this probe allowed for simultaneous determination of hepatic venous oxygen saturation, hemoglobin and hepatic tissue pH with near infrared spectroscopy during hemorrhagic shock.

Specific Aim 1: To develop near infrared (NIR) spectroscopic techniques to measure peripheral muscle pH in the surgical intensive care unit and evaluate the potential of this method as a predictor of multiple organ dysfunction syndrome (MODS) and a guide for resuscitation.

Progress: The team is awaiting Partners Risk Assessment for human studies.

Specific Aim 2: Validation of NIR tissue pH measurement. The original plan for an NMR experiment was modified to a study the swine liver. The team seeks to demonstrate that tissue pH is an indicator of anaerobic metabolism and a measure of liver function and therefore can serve as a valuable indicator of shock and adequate resuscitation of critical organs. Liver pH could be measured at the bedside either endoscopically through delivery of a fiber optic probe or noninvasively through the skin.

Progress: A laparotomy is performed and catheters placed in the bile duct and hepatic vein and pH electrodes and Diametrics Paratrend sensors in the liver. When available, pH electrodes and Diametrics sensors are also placed in the flank muscle. After a 60 minute stabilization period, animals are randomized to a sham or shock group. If the pig is in a shock group, hemorrhage is initiated by bleeding the pig over 15 minutes to a systolic blood pressure of 40 mm Hg. Shock is maintained for either 30, 60 or 90 minutes and the pig is resuscitated with saline and followed for 2 hours. The team is planning on doing 5 pigs in each group, a total of 20 pigs.

Tissue pH, PCO_2, PO_2 and NIR spectra of the liver are recorded every 10 seconds. A blood sample is collected every 5 minutes and hepatic vein oxygen saturation and hemoglobin is measured. Bile is collected every 30 minutes. At baseline, end of shock, and end of recovery a biopsy is collected from the liver, as is blood from the hepatic vein and femoral artery. Anaerobic metabolism will be assessed by measuring the lactate concentration and the onset of dysoxia. Liver function will be assessed by AST production, the rate of bile production, tissue necrosis and apoptosis and the clearance of

indocyanine green (ICG) at the end of the experiment by monitoring directly on the surface of the liver.

All of the animal surgery (24 pigs) has been completed to conclude the development of the *in situ* ICG monitor and to test the performance of the NIR models. Resuscitation results from eligible animals were analyzed. The team tested the hypothesis that resuscitation that fails to restore tissue pH above 7.19 or tissue PCO_2 below 76 (the critical levels indicating dysoxia) will be indicative of liver injury.

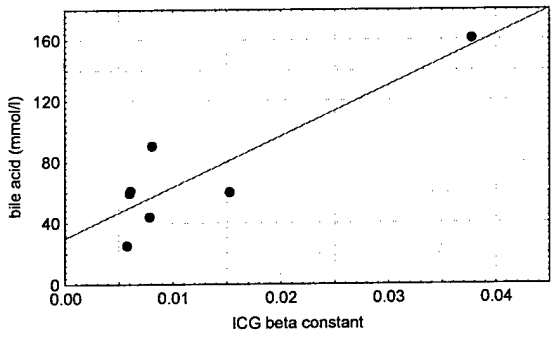
Data from 18 animals qualified for analysis. Animals which died after resuscitation or had AST levels > 100 IU were classified as unsuccessfully resuscitated. Association between failed resuscitation and tissue pH below or PCO_2 above the critical level at the end of recovery was determined with a Fisher exact test. Four animals were not successfully resuscitated. The table compares tissue pH and PCO_2 for animals which were successfully and unsuccessfully resuscitated.

	Failed Resuscitation (n = 4)			Successful Resuscitation (n = 14)		
	Baseline	Shock	Recovery	Baseline	Shock	Recovery
pH	7.31 ± 0.01	6.84 ± 0.12	7.02 ± 0.15	7.38 ± 0.01	7.24 ± 0.02	7.29 ± 0.03
PCO_2	64 ± 4	139 ± 35	97 ± 35	52 ± 2	67 ± 3	52 ± 3

Tissue pH < 7.19 at the end of recovery was significantly associated with failed recovery ($p = 0.04$) with a sensitivity of 0.75 and a specificity of 0.86. Also, tissue PCO_2 >76 was significantly associated with unsuccessful resuscitation ($p = 0.04$), with a sensitivity of 0.5 and a specificity of 1.0. This data indicates that restoration of hepatic tissue pH above or tissue PCO_2 below the critical value may be a useful indicator of successful resuscitative therapy.

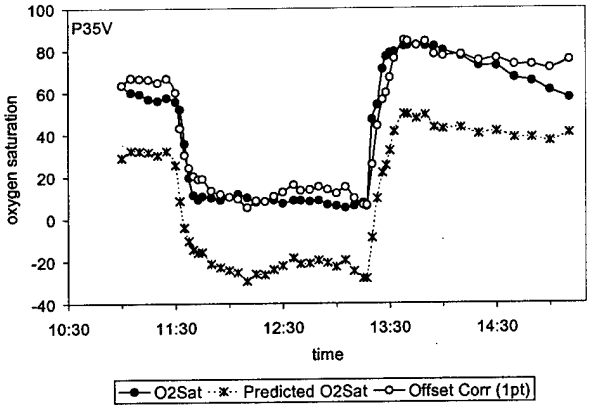
In situ ICG monitoring to assess liver function:

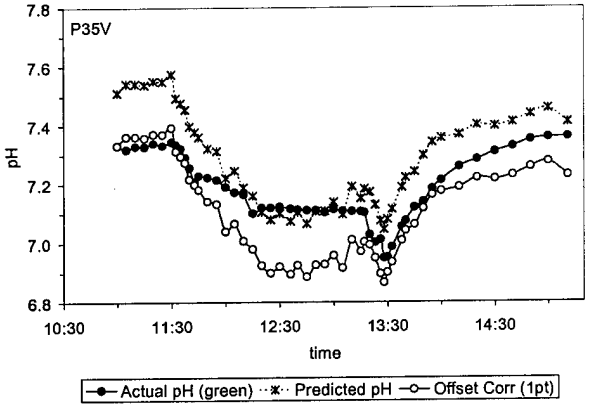
ICG clearance data from 9 pigs (3 sham, 3 - 60 minute shock and 3 - 90 minute shock) at the end of the 2 hour recovery period was successfully collected. With the fiber optic probe used to collect NIR data for pH and S_vO_2 measurements, the concentration of ICG in liver tissue was measured as it was taken up by the liver and excreted into the bile. By fitting a bi-exponential curve to the data rate constants for ICG uptake, α, and ICG excretion, β, could be calculated. It has been previously shown that the β constant is sensitive to changes in liver function as a result of hemorrhagic shock (Shinohara et. al. Heptology 1996; 23:137-144). It was found that the β's determined in this study were well correlated with 2 other sensitive measure of liver function, the level of bile acid ($R^2 = 0.78$, $p = 0.008$) and phospholipid ($R^2 = 0.92$, $p = 0.0007$) found in the bile at the end of resuscitation. These data indicate that the in-situ monitoring of ICG directly on the liver provides a sensitive assessment of early liver dysfunction.



NIR measurement of hepatic S_vO_2 and tissue pH:

PLS was used to develop calibration models to determine hepatic venous SO_2 and tissue pH from any pig. A model for S_vO_2 was built using data from 16 pigs over the wavelength range 380 – 1100 nm. The model had 12 factors, and after offset correction demonstrated an average R^2 of 0.81 and an SEP of 10. The average offset was less than 1, but the range of values for the 16 pigs was –18 to 17. A pH model was built with data from 9 pigs over the wavelength range 600 – 900 nm. The model had 15 factors, and after offset correction demonstrated an average R^2 of 0.70 and an SEP of 0.05. The average offset was 0.06 with a range of –0.17 to 0.35 pH units.





These models were used to measure liver tissue pH and hepatic venous oxygenation from spectra collected from 4 other pigs not used for model development. The actual and NIR measured data are shown in the attached figure. Data is also presented for calculated values which are offset corrected from a blood draw or pH reading taken at the first point. The offset-corrected oxygen saturation results are very good and within the predicted error for 3 of the 4 pigs. The pH results are not as good, though trends are obvious and sensitivity to small pH changes, particularly upon reperfusion, is evident. Differences between electrode and NIR measured pH might be due to real heterogeneity in tissue pH and not necessarily to poor model performance, particularly for P36V, where electrode pH recovers, but NIR pH doesn't.

It was hoped that these models would not need offset correction, since the liver was illuminated directly and not through the skin. Possible reasons for the offset are being

investigated, and include angular variation of the fiber optic probe on the soft liver surface and day-to-day variation in the reference spectra.

These data demonstrate that it is possible to use NIR spectroscopy to adequately measure hepatic tissue pH and tissue oxygenation. If laparotomy will be performed, this data is more accurately collected with the Diametrics sensors. Muscle tissue pH correlates well with hepatic tissue pH and AST assessment of liver injury. The next step(s) in developing a tool to noninvasively assess splanchnic underperfusion will be the continued development of a technique for NIR measurement of muscle pH and oxygenation..

2.5 NEW INITIATIVES CLINICAL FOCUS AREA

The New Initiatives group within CIMIT serves as the point of entry for research in minimally invasive therapy which is outside of the purview of the other clinical focus areas: Cardiovascular Disease, Cancer, Stroke, and Trauma and Critical Care. As such, this Clinical Focus Area is responsible for matching the ongoing needs of entry and intermediate-stage projects. New Initiatives provides an "incubator" function for clinical problems and technologies that are likely to evolve toward minimally invasive treatment. As new approaches are "matured" through the pilot phases of treatment into clinically promising methods, they are spun onto the established (or new) clinical focus areas.

Task 1: Develop a computer based three dimensional imaging treatment planning system to drive an endoscopically placed, miniature, facial skeletal distraction device.

The significance of this project relates to the development of innovative, minimally invasive techniques for surgical treatment of patients with congenital and acquired craniomaxillofacial deformities. The combination of minimally invasive surgical techniques with the design and implementation of buried, miniature distractors guided by computer manipulated 3-D CT data, will increase operator and patient acceptance, and expand the applications of distraction osteogenesis (DO) to a variety of common craniomaxillofacial problems. There is no currently available system for surgical treatment of craniomaxillofacial deformities which links minimally invasive techniques, miniaturization, and a computer based treatment planning program. This concept is unique to the Massachusetts General Hospital, Skeletal Bone Research Center and the BWH Surgical Treatment Planning Laboratory project on DO.

The software developed in the first year of this project allows surgeons to visualize, explore and analyze a number of potential osteotomy alternatives to aid in the decision to perform minimally invasive surgery, and if so, to select the best approach (Everett et al, 2000). Specifically, when combined with existing SPL tools for anatomical segmentation and registration, this tool provides methods for: 1) Pre-surgical evaluation of 3-D diagnostic images including the visualization of 3-D data acquisitions in various modalities and the measurement of anatomical distances and angles; 2) Interactive simulation of osteotomy and planning of surgical movements of the facial skeleton: computation of reference geometry (axes, points, and planes); the simulation of an osteotomy cutting tool (geometry and movement); computation of post-surgical bone volumes; simulated movement of skeletal components with collision; computation of net movement parameters; placement of devices based on movement properties detection; 3) Post-surgical interactive evaluation of the bone movement: anatomical registration with pre-surgical images; measurement of skeletal movement against pre-surgical anatomy and against reference geometry; measurement of new bone volume.

The overall goal of this project is to apply the software application designed in the initial project for planning a variety of clinical cases. The team will use the software to determine the vector of movement, to simulate the shape and location of the osteotomy, to guide placement of the distractor and to analyze the predicted versus the actual surgical result (outcome).

Specific Aim: To develop a computer software application for the planning and simulation of an osteotomy and for analysis of the results. In particular,

- To document reproducibility of the selected landmarks using both "Multiplanar" and "freehand" methods.
- To update the software and make it compatible with the new version of the "Slicer" and "Visualization Tool Kit" of the Surgical Planning Laboratory (SPL)
- To analyze skeletal changes in 25 pre and postoperative patients treated by distraction osteogenesis.
- To apply the software prospectively for treatment planning a selected variety of distraction cases.
- To analyze the outcome of the cases in Specific Aim 1.4 and to modify the software as necessary.
- To make the program more user-friendly for clinicians and accessible as a product.

Progress: The software to store landmark points of the skull and facial skeleton has been created. Pre and postoperative CT scans can now be accurately superimposed. Pre and post-operative position of the skeletal points can be used to calculate vectors of movement.

Appropriate landmarks can be placed (and stored) to correlate standard lateral cephalometric landmarks with 3-dimensional CT landmarks. The 3-dimensional vector of distraction can be prospectively calculated, movement can be predicted and a prescription for distractor design and orientation can be created.

Recently, software to store landmark points has been updated and made compatible with the new (updated) version of the *3Dslicer* and *VTK* (visualization tool kit) and the computer workstation for the MGH has been acquired. This station will interface between the SPL (at BWH) and the MGH. Also, software for collision detection (audible and visual) between bony fragments has been added.

Future Work: The team is currently working on getting the computer workstation at MGH to operate at the same level as that at the SPL at BWH. To accomplish this, the team is developing the required interface.

Concurrent with the aforementioned activities, the team is developing the ability to "prospectively" treatment plan a case. Cases are planned for Oct 2000 and Dec 2000. The team will analyze the outcomes of these cases and modify the software as needed.

The team is also concentrating on assessing the reproducibility of locating bony and constructed landmarks on 3-D CT images using the "Multiplanar" method. Results will

be compared to the "freehand" method. The team also plans to compare lateral cephalometric analysis for a set of cases to the same analysis applied to 3-D images derived from CT data and evaluate the utility of traditional 2-D analysis as compared to 3-D data.

Finally, the team is analyzing skeletal changes in 25 pre and postoperative patients treated by distraction osteogenesis.

Task 2: Lung Volume Reduction Using a Bronchoscopic Approach

The objective of lung volume reduction is to eliminate dysfunctional, overinflated regions of the lung. Results similar to surgical resection have been obtained by plication and stapling without tissue removal, as well as by laser directed tissue ablation. These observations suggest that removal of the dysfunctional tissue is not required. A procedure that eliminated the participation of dysfunctional tissue in the breathing process would suffice.

There have been no detailed studies on the lung mechanical effects of experimental emphysema in large animals. It is useful to know the specific changes in lung mechanics with emphysema induction to deploy the animal model for studies of novel emphysema interventions. Specifically, the team wished to understand the effects of papain to induce emphysema on airway and tissue resistance and elastance, since diseases such as emphysema may harbor both parenchymal and airway abnormalities concomitantly. To do so, the team employed a method of optimal waveform ventilation for measurement of dynamic airway and tissue mechanics, and static measurements of elastic recoil and functional residual capacity. The goal was to demonstrate that parenchymal disease induced by papain was similar to human emphysema. Hence, this project entailed two scientifically novel features: 1) the development of a reproducible model of diffuse emphysema in sheep using aerosols of papain, and 2) the characterization of the disease process using optimal waveform ventilation (OWV) in addition to static mechanics.

Specific Aim 1: To compare short term (1 month) and long term (3 month) survival, physiological responses, surgical complications and lung histopathology in control sheep (untreated, non-emphysema) following either standard surgical plication lung volume reduction or bronchoscopic lung volume reduction (BVR).

Progress: Papain aerosol exposure at the dosages employed resulted in mild-to-moderate changes in static elastance, and reduced airway diameters as assessed by OVW. The disease produced is subclinical, which has distinct advantages, in that confounding problems with unstable nutrition, weight loss, pain and discomfort were not evident. Since the peripheral airways are most susceptible to alterations in elastic recoil pressure, it would be seem reasonable to conclude from the OVW data that peripheral airway constriction is the most significant result. The ovine model therefore simulates many of the changes observed in human emphysema, and is suitable for modeling the disease, for the purpose of further investigations. The activity was successfully completed

Specific Aim 2: To compare short and long term survival, physiological responses, complications, and lung histopathology in sheep with emphysema (generated by papain exposure) treated either with SPVR or BVR.

Progress: Volume reduction therapy (VRT) for emphysema involves removal of hyper-expanded, dysfunctional lung, which increases recoil, improves tethering, and recruits previously compressed lung. This has traditionally been accomplished by surgical means. The team describes a bronchoscopic method of VRT in which fibrin glue containing pro-fibrotic growth factors is used to collapse and scar emphysematous lung. This study concluded that BVR using a fibrin-based glue achieves effective, safe volume reduction in a sheep with emphysema. The activity was successfully completed.

Task 3: Transdermal Drug Delivery and Chemical Sensing for Neonates using Skin Electroporation.

The team has made significant progress with respect to Specific Aim 1, which must be achieved before Specific Aims 2 and 3 are pursued. Both theoretical and experimental results have been obtained with prototype electrode/reservoir devices (ERDs) that demonstrate both transverse and lateral electroporation within the skin's stratum corneum (SC). These findings are in agreement with computer simulations, and provide a mechanistic foundation for devices that essentially will confine all of the externally applied voltage pulses to the interior of the SC.

Specific Aims: Optimize parameters for creation of microconduits in hairless rat skin *in vitro*. Determine transdermal transport of aqueous solution through microconduits *in vivo* in hairless rats. Creation and partial optimization of microconduits in neonatal skin *in vitro*.

Progress: Further computer simulations have been carried out using the well established "brick wall" model of the SC, in which the hydrated corneocytes are the "bricks" and the surrounding multilamellar lipid bilayer membranes are the "mortar". These simulation results show that for the proper choice of electrode/reservoir device (ERD) design parameters, the electroporation is mostly lateral electroporation. This means that voltages and associated currents occur almost entirely within the SC, and can be used with safe keratolytic agents (e.g. sodium thiosulfate + urea, or salicylic acid + benzoic acid + ethanol) provides an approach to electrochemical creation of microconduits without sensation.

Controlled creation of microconduits by this physiochemical method is analogous to electronic microfabrication, in which a first step of microlocalized physical perturbation (e.g. light exposure through a mask) is followed by a chemical removal (e.g. etching by an alkaline solution). This is an exciting prospect: *In situ* engineering of microscopic

pathways penetrating the dead SC, to provide a basis for controlled drug delivery and analyte extraction.

3.0 Advanced Technology Teams

Although clinically driven, CIMIT research requires a large body of sophisticated technical capabilities and new enabling technologies. The program of Advanced Technology Teams (ATTs) has enabled CIMIT to achieve its goal of developing novel therapies that maximize treatment efficacy and minimize patient pain and discomfort. The ten Advanced Technology Teams established in the Proposal for Year 2 served as the foundation from which novel clinical applications were developed. In this context, these ATTs worked closely and synergistically with the Clinical Focus teams described in Section 2 to achieve significant progress towards new minimally invasive diagnostic and therapeutic techniques. Advanced Technology Teams act as a resource for technologically challenging problems within CIMIT, support the technical activities of CFAs, and develop key enabling technologies to increase quality or decrease cost of clinical care.

The research activities that currently comprise the ATTs are described in the following subsections:

- Biomaterials (Langer, MIT)
- Image guided therapy (a new aggregation of the Artificial Intelligence and Surgical Planning ATTs) (Kikinis, BWH)
- MicroSensors (Cunningham, DL)
- Simulation (Dawson, MGH)
- Tissue engineering (Vacanti, MGH)

Collectively, new advancements in these technological areas will lead to major new therapies and treatment modalities.

Others of the originally proposed ATTs are not reported out separately: "Minimally Invasive Interventional Devices" was merged into the Cardiovascular Disease CFA. "Energy Delivery" supports the Cancer CFA project "Early Detection and Ablation of Epithelial Cancers". The work in "Endovascular Tools" has been pending review by the DoD animal use review process; that approval has just been obtained, and a progress report for that project is anticipated in Q9.

3.1 Biomaterials

Advances in minimally invasive techniques will require extensive research in and development of smart "molecular probes", novel biomaterials and artificial tissues. To achieve these advances we have created an Advanced Technology Team on biomaterials. The purpose of this team is to: 1) engage in cutting edge research driven by clinical needs, 2) identify promising new techniques, materials, methods or procedures in the field and efficiently identify mechanism to transfer this technology to clinical use

(translational research) and 3) provide a forum to disseminate information between academia, industry and government.

The impact of molecular and biomaterials research on healthcare has been astounding. For example, the development of slow drug release systems and implantable devices/materials has become a clinical reality. Advances in computer power have enabled molecular modeling to become a useful tool in the design of small molecules with specific molecular action. Despite these recent advances and achievements, the vision of future developments over the next 5-10 years is even more exciting. The development of reporter molecules to image or probe for specific molecular events will become reality. We will furthermore see an exponential growth in the areas of gene therapy where novel gene delivery systems will be required. As more complex therapies evolve, injectable drug carriers will be urgently be needed. Another significant growth area will be the fabrication and implantation of support systems for genetically engineered cells and tissues.

This ATT is uniquely suited to address emerging needs and tackle unique opportunities. Not only do its members have a significant track record of achievements, but a clear vision of the future. Through close interaction with other clinical cores, scientifically relevant strategies will amalgamate with clinically important needs and lead to the development of novel biomaterials and engineering strategies. Furthermore, this ATT will leverage the considerable amount of collaborative research already in place, with MGH's Center for Biomedical Engineering in Oncology (MGH), Center for Engineering in Medicine (MGH/MIT), and the Program in Brain Tumor Gene Therapy (MGH). Well represented expertise exists in the fields of chemistry (analytical, organic, inorganic, polymer, bioconjugate and combinatorial chemistry), molecular and cellular therapeutics (drug delivery systems, slow drug release, targeted therapies, cell transplantation, cell trafficking), genetic engineering (vector design, gene delivery, gene transfer, gene therapy, recombinant protein design, phage display, bacterial and viral engineering), cell biology and tissue culture (transgenic expression, recombinant cells and tissue cultures, microspheres and matrices/support structures for cell growth, preservation of cells and tissues, biomaterials for tissue repair), and clinically relevant aspects of biomaterial use (obstacles to drug delivery, rejection, immunology).

Task 1: Degradable Conductive Polymers

Biodegradable microspheres have the potential to serve as depots for the delivery of DNA for gene therapy. This type of delivery system will be minimally invasive because it can be injected rather than implanted to provide a polymer matrix that will gradually dissolve releasing the therapeutic agent. There is no need to remove the spheres after depletion of the drug. Our goal is to encapsulate DNA that has been complexed with pH sensitive cationic polymers, "proton sponge polymers," that have been shown to enhance the levels of transfection relative to naked DNA.

During the past year the team has accomplished the following:

1) Continued with the scale-up of pyrrole-3-butyric acid. The team has currently scaled-up the procedure to the hydrazone derivative step up to 50-100 gram scale in excellent yield. The team is currently in the process of completing the scale-up to the final product.
2) Continued with experiments to evaluate the feasibility of coupling small polymer moieties such as poly(ethylene oxide) and poly(dl-lactic acid) with pyrrole molecules derivitized at the three position with a butyric acid group. Towards this end, the team has evaluated several reaction conditions that employ DCC/DMAP coupling chemistry in mixed solvent systems such as methylene chloride/DMF with good success. The team is currently exploring the coupling chemistry further.
3) Made significant headway in the synthesis of oligopyrroles (3-5 pyrrole units). The team has so far synthesized tri-pyrrole molecules using pyrrole-2-carboxaldehyde as a starting material. This molecule will serve as the building block for the synthesis of degradable polymers possessing conductive oxidized oligopyrrole moieties.

Specific Aim 1: To synthesize degradable analogs of the conductive polymer PPy, as well as water soluble analogs, and to study the degradation and cytocompatibility characteristics of these polymers.

Progress:
Potential role of electroactive polymers: Electroactive polymers, which constitute a unique class of synthetic polymers, possess the ability to inter-convert chemical, mechanical, thermal and optical perturbations into tiny electrical currents. This property can be exploited to play an important role in the interfacing of the external environment with biological systems. Electronically conductive polymers are especially attractive in that, they can not only be employed as guidance channels or substrates for tissue culture but can also potentially be utilized as a medium to subject the adhered tissue (cells) to an electrical stimulus.

Role of electroactive polymers in nerve regeneration: The role of electromagnetism and electrical currents in the tissue regenerative process is now fairly well accepted. With respect to neuronal tissue, the ability of electromagnetic energy to induce cell migration and differentiation is beginning to be established. Past work has demonstrated that electrical charges and electromagnetic fields play an important role in stimulation of neuronal processes and sprouting of axons at a transected nerve end. The ability to facilitate and enhance the sprouting and migration of growth cones from the damaged nerve end across a gap could have profound consequences in developing new clinical modalities and improving the success of existing clinical therapies for treating PNS and CNS degeneration and damage.

Neuronal cell interaction studies: The team investigated the interaction of PC-12 cells and Schwann cells on various substrates including poly(L-lactic acid)-a biocompatible polymer and conductive substrates such as Indium Tin Oxide (ITO) glass polypyrrole (PPy) thin film containing a polyanionic dopant poly(styrenesulfonate) (PSS). PC-12 cells are similar to primary neuronal cells in that they respond reversibly to soluble nerve growth factor. The team found that PPy was an excellent substrate for both PC-12 and

chick dorsal root ganglial cells attachment and differentiation (Figure 1). Furthermore, the team demonstrated that the application of an electrical stimulus to PC-12 cells adhered onto PPy substrates resulted in a significant increase in the length of neurite extensions (median neurite length for PC-12 cells grown on PPy and subjected to an electrical stimulus was 18.14 μm (N = 5643) compared to 9.5 μm (N = 4440) for controls). Thus, the ability to stimulate neurites extensions (axons) using PPy can have far reaching consequences in restoring function to a region in the body after nerve transection.

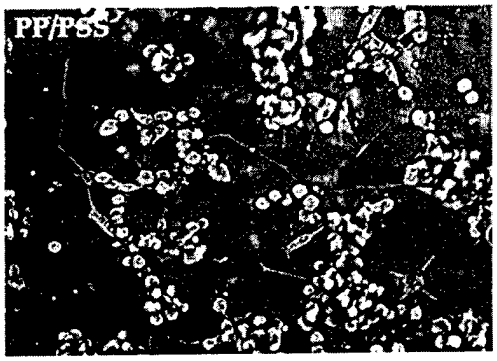


Figure 1

Significance of biodegradable analogs of polypyrrole: Notwithstanding the important role PPy or electronically conducting polymers can potentially play in modulating cellular functions, it would be useful to have it in a more processible form and have it undergo degradation *in vivo*. This would be particularly important for applications wherein a PPy coating is used to alter the surface characteristics or tissue response to a prosthetic for a well-defined period such as coating of a vascular stent to minimize smooth muscle proliferation and restenosis. One can also envision coating of metal or carbon composite or other polymeric orthopedic prosthesis with conductive polymers such as polypyrrole to improve tissue compatibility and adherence of the implant to surrounding tissue. Furthermore, from a tissue-engineering standpoint, it would be ideal if the conductive polymer matrix served as a template for the desired period and underwent degradation thereafter thus eliminating any potential long-term undesirable tissue response.

Also, in the past year, the team has made significant progress in the following five specific areas:

Scale-up of pyrrole-3-butyric acid: The team has continued the scale-up of pyrrole-3-butyric acid successfully up to the hydrazone derivative stage using the synthetic procedure described in Figure 2.

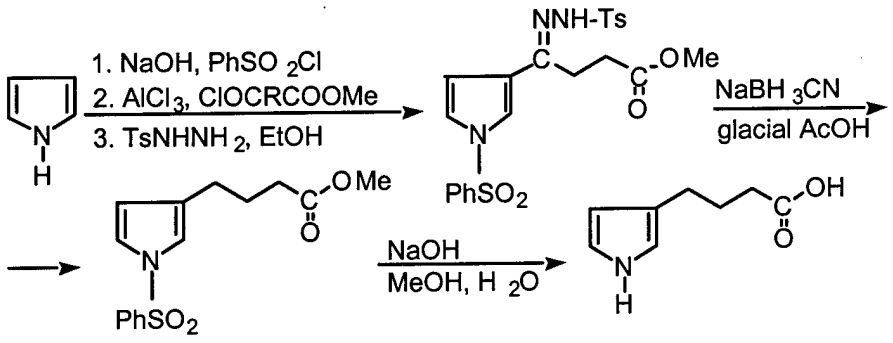


Figure 2

Synthesis of 3- functionalized tri-pyrrole derivatives: The synthesis of the tri-pyrrole derivatives was carried out using the pyrrole-2-carboxaldheyde as a starting material using a modified procedure of Meijer, et al. In order to derivatize the tri-pyrrole in the 2 and 3 position on the terminal pyrrole units, the nitrogen group on the all three pyrrole units have to be protected with protecting groups. The choice of the protecting group is based on the (a) ease of removal and (b) capacity to direct the subsequent alkylation to the desired position. In view of this tertiary butyl carbonate (t-BOC), which is an acid labile protecting group and phenylsulfonyl ($PhSO_2$), which is capable of directing the alkylation specifically to the 3-position were chosen and tri-pyrrole units wherein all the 3 nitrogen atoms were protected with either t-BOC or $PhSO_2$ were synthesized.

Synthesis of poly(dl-lactic-co-glycolic acid)(PLGA) and poly(ethylene glycol)(PEG) coupled to pyrrole-3-butyric acid: The team has successfully coupled PLGA and PEG of molecular weights ranging from 10-30 KDa and 500-10,000 respectively, with pyrrole-3-butyric acid using DCC/DMAP chemistry. The resulting polymers possess a polymerizable pyrrole unit at either extremity that is capable of undergoing oxidative chemical polymerization. The team has polymerized these polymers using ferric chloride in mixed solvent systems such as water/acetonitrile/methylene chloride to yield polymers that possess varying degrees of resistance and solubility. For example, polymers derived from PEG afford water-soluble entities while those derived from PLGA yield organic soluble entities.

Task 2: Polymer-based Gene Delivery Platform

The local delivery of gene therapeutics via minimally invasive modalities, such as through catheters, endoscopes, or laparoscopes for the treatment of vascular, gastric or hepatic disorders, could lead to the development of real advancements in the field of gene therapy. A particular advantage of local gene therapy is the regionalized expression of

therapeutic protein at the desired site. High levels of gene expression within a desired subset of cells are generally required for local therapeutic levels of protein to be generated. The long term goal of this project is to create a safe synthetic polymeric gene delivery system with high transfection efficiency for local delivery of plasmid DNA.

Over the past year the cationic polymer poly(lysine)-graft-imidazole acetic acid was synthesized to meet the design criteria set out in our goal to develop a cationic polymer with the ability to complex DNA into nanoparticles that could be taken up by cells via endocytosis and mediate transfection. The DNA polymer complexes prepared with this polymer were able to transfect several different cells lines nearly as well as polyethylenimine (PEI) but with considerably less toxicity. Due to the promising results obtained for the imidazole substituted polymers, studies to elucidate the mechanism of the transfection enhancement induced by the incorporation of the imidazole group have begun. Results from these studies will be utilized to further optimize these polymers.

The synthesis of new biodegradable polyamines was investigated, with a focus on the identification of straightforward synthetic routes to structurally unique materials. A family of tertiary amine-containing poly(β-amino esters) was generated from commercially available starting materials in a single synthetic step. These polymers were hydrolytically degradable and demonstrated low toxicities relative to PEI in initial cytotoxicity studies. The polymers interacted electrostatically with plasmid DNA at physiological pH to form soluble DNA/polymer particles with diameters on the order of 50-200 nm. The combination of biodegradability and reduced cytotoxicity for this family of DNA condensing polymers suggested that they may be useful as polymeric transfection vectors. Initial screening studies were promising, although additional studies will be necessary to more rigorously determine their safety and efficacy. An initial report describing this work is currently in press for publication in the *Journal of the American Chemical Society.*

While the impact of these new materials on gene delivery is potentially high, this research is still in its infancy. Further research is necessary prior to their commercialization for clinical use.

Specific Aim 1: To synthesize a polymer-based gene delivery system that on the molecular level mimics viruses, i.e., capable of condensing and encapsulating DNA, entering cells via endocytosis and escaping the endosomal compartment to release the DNA into the cytoplasm.

Progress: After designing and evaluating several generations of imidazole containing polymers, one series has shown promise as a high efficiency gene transferring agent, poly(L-lysine)-graft-imidazole acetate polymers. It is felt necessary to determine what about this series of polymers makes them work and what can be improved upon to gain even higher efficiencies since there is still a long way to go to approach the gene transfer efficiencies observed for many viral vectors. This is being pursued by looking at the ability of these polymers to overcome cellular barriers to transfection.

Important barriers to transfection include; DNA condensation, endocytosis, endosomal escape, nuclear transport and separation of DNA from the carrier. The grafting of imidazole to the poly(L-lysine) backbone may alter this polymer's ability to overcome several of these barriers. Imidazole containing polymers having varying degrees of substitution are being compared to underivatized poly(L-lysine) and the standard "proton sponge polymer", polyethylenimine (PEI).

A new series of poly(lysine)-graft imidazole acetate polymers were synthesized. Polymers were synthesized using three different molecular weight poly(lysines) as starting material (9.4 kD, 34.4 kD and 57.2 kD). For each molecular weight of poly(lysine) a range of polymers having different degrees of imidazole substitution were synthesized. The degree of imidazole substitution ranged from 0 to 95%. Although different degrees of imidazole substitution have been investigated previously, the influence of the molecular weight of the poly(lysine) backbone had not been studied.

Transfection studies in a new cell line, C3A, a derivative of Hep G2 cells, were performed to determine how the molecular weight of polylysine influenced the transfection efficiency of these polymers. These investigations also set the preliminary ground work for measuring the amount of plasmid taken up and trafficked to the nucleus by this cell line using a Real-time PCR assay developed for this cell line. The results of transfection studies done comparing the influence of the molecular weight of the poly(lysine) on the observed production of luciferase by transfected cells is shown in Figure 1. A trend could be seen for underivatized poly(lysine) showing increased luciferase production as molecular weight decreased. This trend was not as apparent for the imidazole substituted polymers. Transfection studies were also done comparing the presence or absence of serum during the time in which the cells are incubated with polymer-DNA complexes. In this cell line, the transfection of cells by PEI was significantly higher than that observed with the imidazole containing polymer however, the PEI was also considerably more toxic to the cells. The presence of serum decreased the observed luciferase production for all types of polymer but the imidazole containing polymers were less affected by the presence of serum than PEI.

The association between the polymers and DNA was indirectly measured by observing the degree of quenching of ethidium bromide as a function of polymer concentration within the complex. The fluorescence of ethidium bromide is quenched when it intercalates into DNA. If the interaction between the DNA and ethidium bromide is disrupted by the presence of the polymer, this will be reflected by a change in the fluorescent intensity of the ethidium bromide. The results of these studies for polymers synthesized with the 9.4 kD poly(lysine) are shown in Figure 2. As the amount of polymer is increased the ethidium bromide fluorescence, relative to the maximum quenching, is found to decrease. This suggests that the DNA becomes less accessible to the fluorescent probe. For highly substituted imidazole containing polymers the DNA begins to become more accessible as the polymer concentration is further increased beyond a point of minimum fluorescence. The mechanism by which this occurs has not yet been elucidated but it is interesting to point out that it is at these higher polymer/DNA weight ratios that the higher transfection efficiency is seen. The forthcoming

investigation of the dissociation behavior of the DNA:polymer complexes will contribute to the understanding of these results.

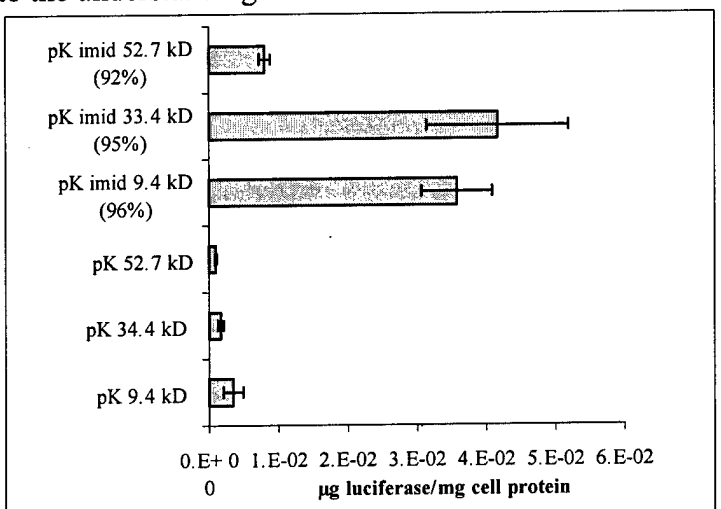


Figure 1: Transfection efficiency of poly(lysine) (pK) and imidazole substituted poly(lysine) (pK imid) as a function of molecular weight of the poly(lysine) backbone. For example, pK imid 52.7 kD (92%), was prepared with poly(lysine) having a molecular weight of 52.7 kD and is 92% substituted with imidazole groups. pK 52.7 kD is underivatized poly(lysine)

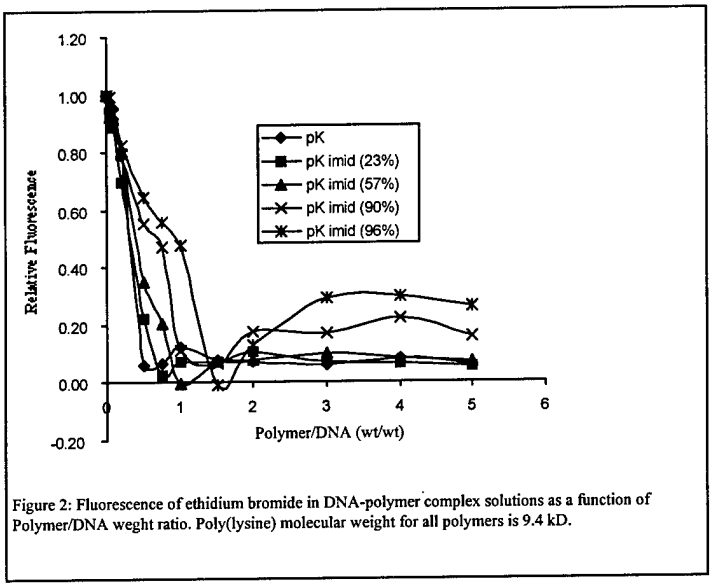


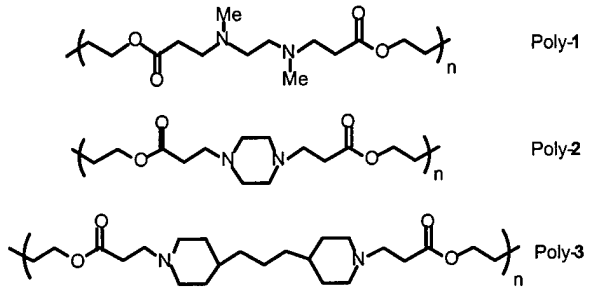
Figure 2: Fluorescence of ethidium bromide in DNA-polymer complex solutions as a function of Polymer/DNA weght ratio. Poly(lysine) molecular weight for all polymers is 9.4 kD.

Future Work: Investigation into the ability of poly(lysine)-graft-imidazole acetate polymers to overcome the barriers to transfection will continue. The extent to which the plasmid is taken up into the cell and trafficked to the nucleus and how this correlates with actual protein expression will be compared within the series of imidazole containing polymers and to PEI. The association and dissociation of the polymers with DNA will also be investigated and correlated with transfection efficiency.

Specific Aim 2: To synthesize a family of new poly(amino esters) to be used as potential gene transfer vectors, and to investigate the degradability, initial cytotoxicity, and the

ability of these polymers to complex and condense DNA into nanometer-scale particles suitable for transfection.

Progress: Poly(β-amino esters) was synthesized from the addition of N,N'-dimethylethylenediamine, piperazine, and 4,4'-trimethylenedipiperidine to 1,4-butanediol diacrylate (polymers **1-3**). Polymerization proceeded exclusively *via* the conjugate addition of the commercially available secondary amines to the bis(acrylate ester) and polymers were isolated in up to 86% yields in a single synthetic step with molecular weights ranging up to 31,200.



Polymers **1-3** degraded hydrolytically in acidic and alkaline media to yield 1,4-butanediol and -amino acid byproducts. The degradation kinetics were investigated at pH 5.1 and 7.4. In general, the polymers degraded more rapidly at pH 7.4 than at pH 5.1 (Figure 3). In initial screening assays, both the polymers and their degradation products were determined to be non-cytotoxic relative to poly(ethylene imine), a polymer conventionally employed as a synthetic transfection vector (Figure 4).

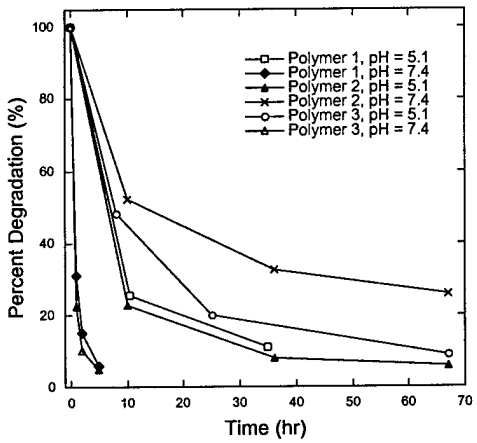


Figure 3

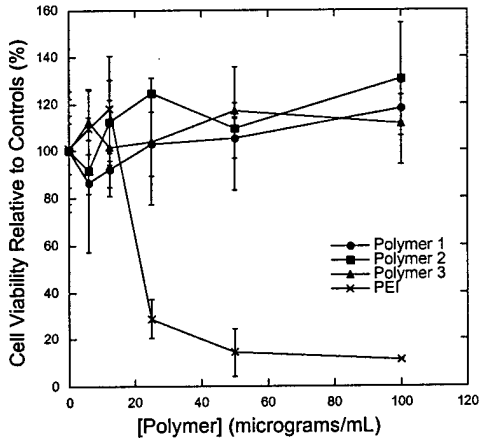


Figure 4

Polymers **1-3** interacted electrostatically with plasmid DNA at physiological pH, as determined by agarose gel electrophoresis, quasi-elastic dynamic light scattering (QELS), and zeta potential measurements. All three polymers condensed DNA into soluble DNA/polymer particles on the order of 50-200 nm. Particles formed from polymers **1** and **2** aggregated extensively, while particles formed from polymer **3** exhibited positive ζ-potentials (eg, +10 to +15 mV) and did not aggregate for up to 18 hours. Initial

screening assays with NIH 3T3 cells suggested that complexes formed from polymer **3** may be useful as degradable polymeric gene transfer vectors. An initial report describing the synthesis and characterization of polymers **1-3** and their complexation with DNA is currently in press for publication in the *Journal of the American Chemical Society.*

3.2 Image Guided Therapy

Image guided therapy is changing the practice of surgery in a fundamental way, by augmenting the direct or videoscopic view that "sees the treated surface" with deeper synthetic imaging modalities that will "guide and measure treatments beneath the surface." This change has been driven by parallel thrusts in the development of new imaging techniques and new therapeutic end-effectors.

Imaging techniques have evolved from X-ray fluoroscopy and B-scan ultrasound to include modalities which differentiate various tissue types (CT, MRI), and measure flow (Doppler ultrasound, MR angiography), cortical function (fMRI), and metabolic activity (PET, SPECT, MR Spectroscopy). Increases in the speed and resolution of these systems have kept pace, so that procedures are now being performed under real time image guidance in "open" MR and CT systems. Rapid advances in 3D volumetric rendering, registration, and automated image processing are facilitating the use of these image data to plan, simulate, monitor, and control interventional and surgical procedures in real time.

Minimally invasive procedures have undergone a similar revolution, beginning with the development of interventional vascular procedures like angioplasty, embolization and stent placement and culminating in extensive current activity in localized ablation techniques such as laser, cryo, electromagnetic, and ultrasound- treatment, as well as local chemical or radioactive methods like ethanol injection or brachytherapy. CT, ultrasound, and MRI have been used for anatomical positioning of these approaches, as well as the guidance of localized biopsy. MRI has been particularly useful due to its abilities to differentiate soft tissue types and to directly image thermal changes, thus enabling direct control of thermal therapies.

Task 1: Segmentation of Bone From CT and Vessels From MRA Data

This project has developed segmentation techniques based on theories from adaptive filtering. The deliverable for the first year of this project, an image feature enhancement scheme for segmentation, is now implemented in optimized C-code. On a standard Sun workstation (SUN Ultra 80) the computational time for a normally sized 3D medical data set is about 3 min, which should be compared to the time for our initial implementation, 20 hours (400 times faster). The new implementation takes advantage of multi-CPU machines via threading which enables increased performance when necessary.

The work in this project aims at developing technology that can be integrated into clinical applications. The project is currently collaborating on generating anatomical models from medical data for three clinical projects within CIMIT: 1) CIMIT Craniofacial: ``Endoscopically Assisted Mandibular Distraction Osteogenesis" for generation of patient specific bone and teeth models from CT data (PI, Dr. Leonard B. Kaban, MGH), 2) CIMIT Simulation: ``CIMIT Simulation Program" headed by Dr. Steven Dawson, MGH, on generation of vessel models from CTA data, and 3) CIMIT Cardiac Robots: ``Virtual Fixtures for Robot-Assisted Minimally-Invasive Cardiac Surgery", PI, Robert D. Howe, PhD, Harvard University. An overview of these collaborations is shown in Figure 1. The nature of Image Guided Therapy is infrastructural where general tools are developed that provide a basis for further development and adaptation in specific clinical applications.

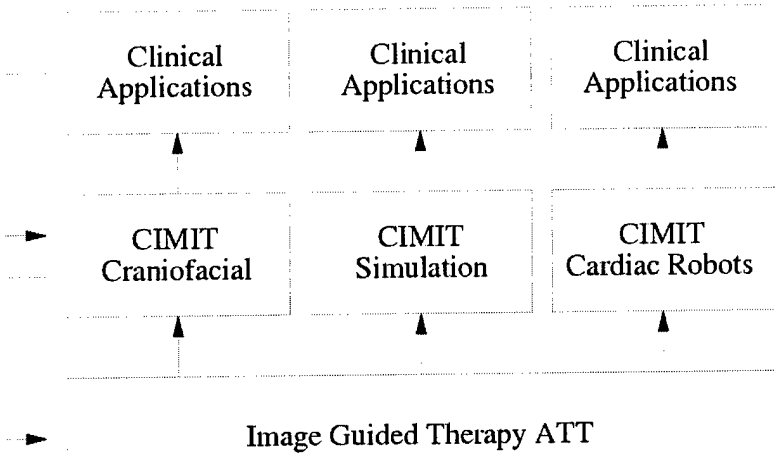


Figure 1. Overview of the current interaction with other CIMIT related projects. The Image Guided Therapy is interacting with several CIMIT projects in creating patient specific computer models from MR and CT data.

Specific Aim 1: To implement a data enhancement scheme for segmentation of bone from CT and vessels from MRA.

Progress: When the project started in February 1999, a first version of the enhancement scheme was already implemented in a high-level computer language, Matlab (from Mathworks Inc). The task was to convert this implementation into efficient C-code to make the system usable in a clinical setting where computational time often is critical. The new implementation was divided into in three major steps: 1) a straight forward conversion to C-code to get a working test bed, 2) testing of algorithmic alternatives to maximize speed while minimizing computer memory requirements, and 3) to adapt the code to make use of multiple processors, if available.

The second step was the most difficult step; several different versions of the code were developed. The major issue was whether the filtering should be performed in the frequency domain or in the spatial domain. Filter theory states that for large filters the frequency domain implementation is more efficient. Since the filters in our application are large, a complete frequency domain based implementation was first developed. The

predicted increase in speed was not obtained. Due to the large nature of medical image data, the memory requirements for running this system were huge (several Gb). Next a spatial domain implementation was developed which provided a faster solution. While the work on validation and tuning of the algorithms continued (see Specific Aim 2) the team investigated methods to reduce the memory use required for a frequency based method, since this method theoretically should provide a faster implementation. A division of the algorithm into independent parts and saving intermediate results to disk during computation gave a considerable increase in speed using the frequency based implementation. With this new data management procedure, the memory model was reduced to a manageable 130 Mb for a single CPU machine. The more efficient implementation has significantly reduced the computation time of the algorithm. The conclusion is that although the FFT version theoretically is faster than direct implementation of convolution, in practice the performance is only better if the memory model is made reasonable. Finally, to make the algorithm usable in a clinical setting, the code was adapted using routines for shared-memory threads on SMP hardware. The computational time is currently 3 minutes for a typically sized 3D data set (256x256x60 voxels) with a memory model of less than 100 Mb on a Sun Ultra 80, with 4 CPU's and 2 Gb of RAM. The project was completed.

Specific Aim 2: Optimization and Validation: to quantitatively validate and optimize the automated segmentation method results.

Progress: The team found that the parameters that most affected the overall performance of the adaptive filtering scheme are: 1) the transition frequency between the low-pass and the high-pass filters, and 2) the noise level parameter that defines noise and image structure in the data.

Selection of the data for validation was performed in close collaboration with our clinical partners. A few slices in each of the data sets were selected and then, critical areas on these slices were outlined. This provided a gold standard that was used as a criterion for finding optimized parameter settings. The semi-automatic procedures used in our Surgical Planning Laboratory today (thresholding, connectivity, cleaning and mending in volume editor) served as a reference. Figure 2 shows the comparison of the automated segmentation and the manual segmentation. Notice the improved vessel continuity and depiction of small vessels in the result from the automated segmentation.

Figure 2: Left to right: Maximum intensity projection of raw data, segmentation by adaptive filtering and thresholding, manual segmentation, combination image showing the differences between the segmentations.

In the final validation study, the team also compared the segmentation of different resolution scans. MRA scans were acquired with different resolution, both in a 0.5T MR scanner (GE Open Magnet at BWH) and a 1.5T MR scanner (GE system at BWH). All scans were carefully, manually segmented by a neurosurgeon.

Future Work:

Segmentation by surface evolution. The team has recently developed the CURVES system, which segments vessels from MRA images by evolving an initial estimate toward the true structures in the image using the codimension-two regularization force This novel regularization force enables the segmentation of very thin structures that would not be possible with a traditional codimension-one evolution. The team has written a preliminary implementation of surface evolution in codimension-two and has preliminary results of segmenting vessels from MRA data. Preliminary observations have been that direct implementation of the level set method is numerically unstable at the zero level set, which is the curve of interest. Therefore, instead of evolving the function directly, the team considers the evolution of its epsilon level set, a tubular surface. Even though results are very encouraging, many points need to be studied in greater detail. The team needs to investigate further the properties of the method such as convergence and the influence of the choice of the initial curve and the choice of epsilon on the results.

A symbolic model description of vessels: The team plans to develop a symbolic description of vessel anatomy based on vessel mid-lines, vessel diameters, and branching points. This would provide a powerful description of anatomy useful for interaction with higher level systems, such as a surgical simulator. Once the data has been segmented, the distance function from the codimension-two surface evolution provides additional information that can be exploited. The team plans to identify the ridges of the negative distance values (inside the vessels). This will provide us with a new, robust way to find the skeleton of the vessel tree. Skeletons are useful for things such as anatomical labeling, automatic path generation for virtual endoscopic fly-through simulations, and estimation of vessel length needed for placements of stents.

Task 2: Real-time Registration of Intra-operative Ultrasound with Pre-operative CT/MR for Image-Guided Therapy

The utility of minimally invasive therapy depends, in no small measure, on the ability to precisely deliver therapy to the targeted site. The efficacy of image guided therapies is now well documented in the literature for such applications as tissue biopsy, cryotherapy, brachytherapy, and energy delivery. For the most part, however, image guidance requires expensive intra-operative equipment (e.g., intra-operative MRI), ionizing radiation (e.g., fluoroscopy, CT), or is limited to surface (e.g., luminal) imaging of areas accessible through videoendoscopic tools. Although inexpensive, non-ionizing, subsurface-capable, and portable, ultrasound imaging has not found the widespread usage that one might expect, due largely to the poor-contrast, specular noise, and unintuitive nature of ultrasound imagery. In this proposal the team aimed to demonstrate a novel new method for improving the visualization quality of intra-operative ultrasound imagery. Specifically, because of the overwhelming preference of users for high-contrast CT/MR imagery, and since such imagery are frequently acquired pre-operatively, the team aimed to demonstrate the ability to register these high contrast pre-operative imagery to yield the same view as the intra-operative ultrasound. The approach enabled, effectively, an intra-operative CT/MR imagery from which image guidance can be performed, but without incurring the costs and risks associated with continuous CT/MR imaging.

The goal of this project was to demonstrate the ability to deform pre-operative CT/MR images, in a non-real time manner, so that point-to-point correspondence to an intra-operative ultrasound can be obtained. This was readily achieved in the first phase of the project for analog ultrasound and CT images of abdominal region containing liver tumor. The demonstration involved enhancement of the ultrasound and CT images, extraction of robust edge-feature images, registration of the edge-feature images involving estimation of the mapping function between the two different types of images and the fusion of the two images. Similar demonstration was attempted on the digital ultrasound data in the second phase of the program. Application of the edge feature extraction procedure, developed for the analog ultrasound data, yielded however disappointing results. Digital ultrasound data did not have enough contrast in comparison to the analog data to yield robust edges of sufficient strength for use in image registration. The efforts were then directed towards the modification of the image enhancement and edge-feature extraction algorithm that would be geared towards the extraction of weak edges. Modification of the algorithm based on prescribed anisotropic smoothness characteristics for the enhanced image and edge-feature images however did not produce any improvement in the edge extraction. It was felt that any further attempts for enhanced feature extraction for a data with inherently weak contrast would lead to more involved and complex processing and thus detract from the ultimate goal of real time implementation.

The 3-D CT/MR registration of prostate data was achieved by using point correspondences and a polynomial warping algorithm to create a dense deformation field, which was used to transform the patients' MR data to an atlas CT image. The team created an error analysis algorithm in which the team placed a set of corresponding points on reserve and used a separate set of points to compute the registration. The interpolated

dense deformation field was then applied to the reserve points and error analysis was performed. The parameters which the team varied were polynomial order, quantity of point set data, and type of point distribution. Based upon our calculations, the team concluded that the 2nd order polynomial was sufficient for minimizing the error in the registration calculations. This implies that fewer corresponding points can be used to compute an accurate registration. Also, the team showed that a horizontally inclined correspondence distribution produced the minimum mean calculation compared to using any of the distributions tested in our research.

Specific Aim 1: Demonstrate the ability to register pre-operative CT/MR, in a non-real-time manner, so that point-to-point correspondence to an intra-operative ultrasound can be obtained.

Progress: A number of parameters could vary in the calculation of phase congruency for edge extraction in ultrasound liver data. The team's choice of parameters for ultrasound organ boundary detection is provided below. The team conducted numerous trials with filter wavelengths ranging from 3 to 20 pixels, wavelet scales ranging from 3 to 5, and the fractional measure of frequency spread ranging from 0.4 to 0.6. The team investigated the edge-feature extraction algorithm and reported on its robustness to high speckle noise content and low contrast in ultrasound liver data in a non-real-time manner. Stages were as follows:

- The team determined an initial filter wavelength of 10 pixels which were analyzed in multiples of the scaling factor (3) between successive filters,
- The team analyzed 4 wavelet scales,
- Six orientations between 0 and 180 degrees were analyzed in increments of 30 degrees,
- The fractional measure of the frequency spread was analyzed at 0.4,
- The number of standard deviations of the noise energy beyond the mean used to set the noise threshold was 2,
- The ratio of angular interval between filter orientations was 1.2,
- The ratio of the standard deviation of the Gaussian describing the log Gabor filter's transfer function in the frequency domain to the filter center frequency was set to 0.55, and
- A factor of 10 was used to control the sharpness in the sigmoid function used to weight phase congruency and frequency spread.

Upon computing the phase congruency at each filter orientation, non-maximal suppression was applied to the image to thin the ridges of the gradient magnitude by suppressing all values along the line of the gradient that were not peak values of the ridge. Non-maximal suppression takes a radius as input whose distance in pixel units are viewed on each side of each pixel when determining whether it is a local maxima or not.

The team concluded that the edge-feature extraction algorithm provided a substantial improvement for ultrasound liver data edge detection compared to the Canny detector. The speckle content was sufficiently minimized and organ boundaries that were not visible using the Canny method became apparent. Almost the entire boundary of the liver

is detected in Figure 1 using our defined parameters including the wavelength of 10. The liver is the large elliptical shaped object in the lower left hand area of the ultrasound images and it encompasses approximately one quarter of the entire ultrasound image. The team notes that small segments of the liver boundary are missing in the edge results which may have resulted from over thresholding the image at the cost of reducing speckle noise detection. The team believes that the results provide a reasonable compromise between edge detection and reduction of speckle noise.

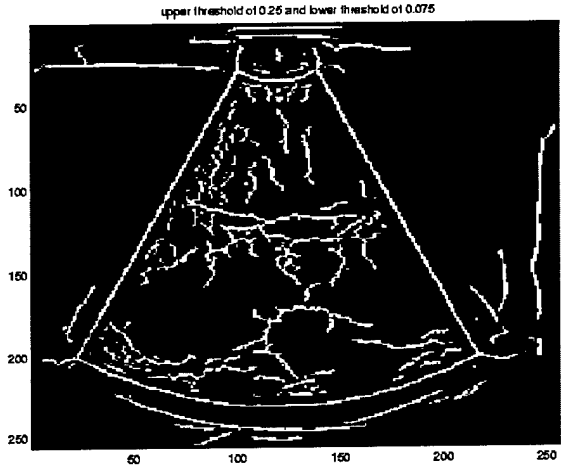


Figure 1

Specific Aim 2: Select a set of surface points from MR/CT, and use ICP to match the points to edges in ultrasound. This result provides an initial correspondence between the two data sets.

Progress: Chui and Rangarajan proposed an alternative to ICP called the Mixture Point Matching Algorithm (MPM), which can solve for both rigid and high-dimensional (thin-plate spline-based) non-rigid transformations between points sets in the presence of noise and outliers. The algorithm is similar to the Expectation Maximization algorithm and jointly solves for feature correspondence as well as geometric transformations. The mixture point matching framework is designed to be general and can be applied to both rigid and non-rigid point sets. The algorithm is similar to ICP however, ICP treats the corresponding points as binary rather than probabilistic variables. The team plans to investigate and test MPM's performance on ultrasound and CT data in future analysis however, the team will continue with ICP for results in this thesis.

Using Chui and Rangarajan's demo intended to compare ICP and MPM results on simulated and sulcal point sets, the team tested ICP on various corresponding point sets in the abdominal area. Figure 2 and Figure 3 contain corresponding points from ultrasound and CT along with ICP results (ultrasound (open areas) and CT (closed areas)) and thin-plate spline warping results, which are located directly below the corresponding ultrasound and CT image.

The team concluded from the non-rigid point experiments that ICP did encounter problems when attempting to find the non-rigid transformation between multi-modal image data. In each of the experiments, ICP did not always find the correct match between each point in the ultrasound and CT point sets. This observation calls for a further investigation into ICP, MPM, and possibly other algorithms that will produce the most accurate correspondence between the data sets.

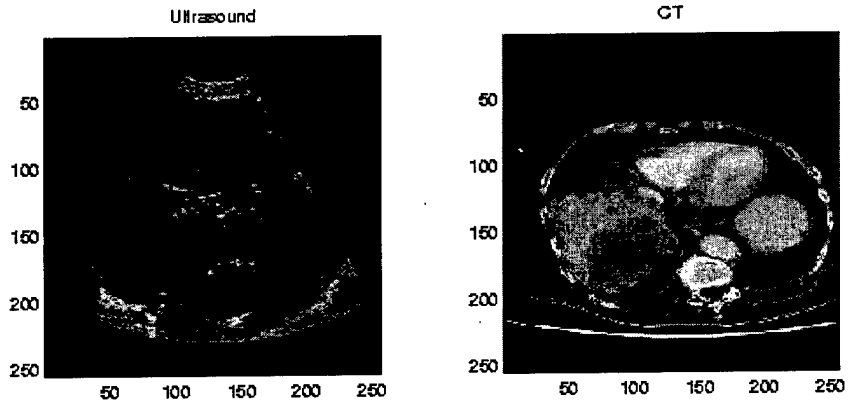


Figure 2

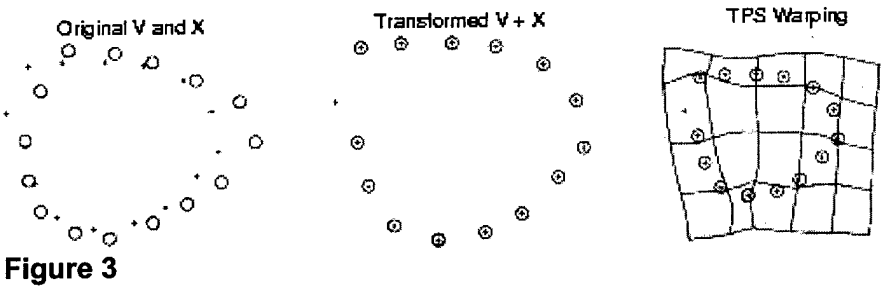


Figure 3

Specific Aim 2: Explore variations on polynomial warping methods which include the following: variation of the number of corresponding points; variation of polynomial order; variation of the point set distribution; and error verification to measure sensitivity in our computed registration errors.

Progress: A precise quantitative study of registration results is deemed necessary for most clinical applications. The team manually located 534 point correspondences in a 3-D CT/MR data set and together with the team at Brigham and Women's Hospital, they used an elastic warping algorithm to register the two modalities. A sparse deformation field, calculated from the corresponding points, was resampled by a factor of 8 to reduce computation time. The team found that the resampling factor had no significant effect on the registration results. The elastic transformation was computed by interpolating the sparse deformation field over the entire volume using polynomials. Additional linear interpolation was applied to produce a dense deformation field the same size as the atlas image. In this analysis, the team sought to explore numerous variations on polynomial warping methods which included the following: variation of the number of corresponding points; variation of polynomial order; variation of the point set distribution; and error verification to measure sensitivity in our computed registration errors.

Using our Error Analysis Algorithm, the team computed the mean error, standard deviation, maximum error, and median error of the Euclidean distances between the transformed points and their actual location in the image. The team observed polynomial orders 1 through 5 for *original* point sets consisting of 263, 176, 132, and 106 points and the respective *reserve* point sets consisting of 132, 88, 66, and 53 points for each of the four experiments. Because the least error in our calculations stemmed from computing the 2nd order polynomial with 66 *reserve* points and 132 *original* points, the team decided to compare those results with a ``ground truth" experiment. This ``ground truth" result was used to compare results of computing the deformation field with all 526 corresponding points versus a sample consisting of 132 points. The team proceeded with a 2nd order polynomial calculation of a data set with no sampling, which produced mean error and standard deviation values of 9.301 and 4.793 voxels.

A comparison of the registration results of the two data sets is provided by a difference image in Figure 4. The difference image confirms that the registration results involving 526 *original* points versus 132 *original* points are not equivalent as expected from the calculated error results but, are quite similar. This result implies that fewer points can be used to compute the deformation field for registration of CT/MR.

The team also conducted experiments to calculate and visualize errors for which registration was computed from clustered point distributions versus the evenly sampled point distributions evaluated in previous experiments.

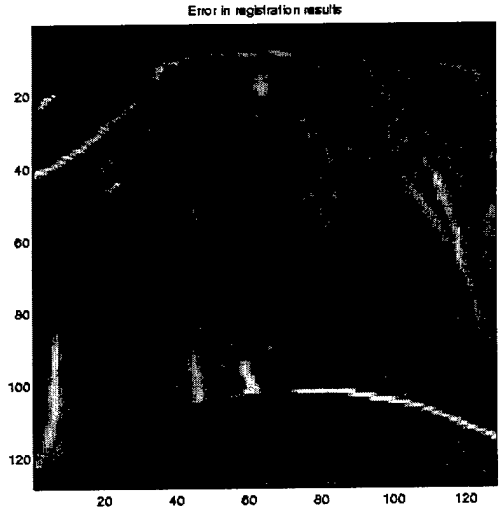


Figure 4

The result in Figure 4 implies that fewer corresponding points can be used to compute an accurate registration. Also, the team showed that a horizontally inclined correspondence distribution produced the minimum mean error calculation compared to using any of the distributions tested in this thesis. The project was completed.

3.3 Microsensors ATT

Background and Significance

Minimally invasive therapy requires the ability to sense problems within the body, to gain access to that part of the anatomy, and to perform some procedure at the problem site. In the future, much of the sensing will likely be performed using small sensors ingested or injected into the body. The aim of the ATT on Miniaturized Sensors and Devices is to maintain a knowledge base of suitable devices and their corresponding phenomenon, and to develop a spectrum of clinically useful devices so as to enable accurate diagnosis, sensing, actuation, and interventions in a minimally invasive manner.

One focus of this ATT is the development of micro-electro-mechanical (MEM) devices; these include gyroscopes, accelerometers, chemical sensors, pumps, motors, vibration sensors, and actuators. It is no longer science fiction to consider a sub-millimeter-sized device that can, for example, use its gyros and accelerometers for navigation, use external RF energy for power, guide itself to the site of a tumor, confirm the diseased area through the use of chemical sensors, telemeter the information to a physician for confirmation, and releases toxic chemicals to destroy the tumor. Sensors that react to biomolecules (e.g., proteins) can also be used to provide real-time feedback regarding the extent of cellular death as a monitoring mechanism. Many of the components in this scenario have already been demonstrated using MEMS technology, although no single "system" endowed with such sophistication has been developed yet.

Task 1: Real-Time Blood Assay

The impact of microbial pathogens on human health, and the potential of a germ-warfare attack, underscores the need for rapid, sensitive microbial pathogen detection and identification. There is a need for methods to detect biological weapons, such as anthrax (*Bacillus anthracis*) and to perform a high-throughput screen of pathogens for development of vaccines and antibiotics. Technology developed to meet these needs may also be applied to monitoring the status of trauma patients. The sensor is a micro-electro-mechanical silicon (MEMS) membrane resonator called the "micro Chemical Analysis Array" (μCANARY) that acts as a miniature, all-electronic platform for performing direct biochemical and microbiologic assays. Affinity ligand reagents that selectively adsorb a particular target analyte from the fluid sample are applied to the μCANARY, which registers a shift in resonant frequency when the mass of the target analyte is incorporated into the receptor coating. Using this method, mass detection of ~10 picograms can be measured, corresponding to a resolution of 0.25 nanograms/ml of a typical antibody in aqueous solution.

The original project application was the determination of cytokines in the blood serum or urine of a trauma victim that predict Multiple Organ Failure (MOF). The trauma team at BWH identified several interleukins whose elevated concentrations have been found to

correlate positively with MOF. Over this past year the goal of the project was expanded to include the recognition of microbial pathogens in body fluids. This capitalizes on the recently demonstrated ability to "fingerprint" microbial pathogens with the MicroCANARY sensor technology. This demonstration of direct-read, near real-time detection and identification of human pathogens has the potential to revolutionize diagnostic microbiology; moving from culture-based methods to a highly specific detection/ identification approach which discriminates pathogens with high sensitivity in a short period of time.

The goal of the project is development of a microarray sensor technology that is capable of measuring a detailed signature profile of blood components in near real-time. Components under investigation include both soluble proteins and microbial pathogens. The project is driven by the need of ICUs to obtain more detailed, timely information on the metabolic, inflammatory, or infectious state of a patient to make decisions on their treatment. The interests of the BWH surgical ICU, directed by Dr. Juan Carlos Puyana, combined with the recently demonstrated ability to "fingerprint" microbial pathogens with our sensor technology, dictate that future focus will be placed primarily upon detection and identification of blood-borne infectious disease. If successful, the "microbial fingerprinting" technique under development will revolutionize diagnostic microbiology from current culture-based methods to a detection/identification approach that is highly specific in its ability to discriminate pathogens with a technology platform than can provide sensitive measurements in a short period of time.

Development of a bioassay for pathogen detection based on phage-displayed affinity ligand reagents (ALRs) was accomplished. In addition, the team focused on the development of hardware and software. First, the team introduced the approach of using phage that has been developed to target the microbial pathogens of interest as the detection mechanism for the 9-element μCANARY sensor. Draper Laboratory conducted the bioassay experiments with Dr. Mark Klempner at New England Medical Center (NEMC). Secondly, hardware and software for the μCANARY sensor array technology was improved, including packaging and testing of the first 9-element μCANARY sensor.

In recent work, the team continued efforts on the development of sensor hardware and software and development of the microdroplet applicator (a BioDot^{TM} instrument) for accurate and precise addressing of individual sensor elements. First, hardware and software for the μCANARY sensor array technology was improved further. Fabrication, packaging, and device characterization of 27 nine-element sensor arrays has been completed using the optimal device and package design. Improvements to the electronic/software architecture used to query the sensor array and display measurements have been completed. In addition, new data analysis mechanisms to minimize temperature effects and electronic drift through common mode subtraction to give a ten-fold improvement in noise reduction (i.e. improved sensitivity) have been completed. The current LabView program enables sequential monitoring (open loop mode) of multiple elements of the sensor array continuously (for any specified time frame), and display of a ΔFsensor-ref in real time. Next, the team plans to further reduce sampling

time and improve signal averaging through construction of a phase locked oscillator circuit for closed loop mode sampling. Secondly, an extensive library of programs was written for the BioDotTM instrument for dispensing reagents on in an array format on planar substrates as well as reagents into individual sensor elements of the 9-element μCANARY. Precision and accuracy (volume dispensed and spatial location) for both applications was verified. These procedures will be applied to 9-element μCANARY-based microbial fingerprinting experiments to detect strains of *enterococci* bacteria. It is also noteworthy that there was significant progress made in establishing molecular biology research capability at Draper Laboratory with hiring of a molecular biologist, Krista Ernewein, and completion of a BL-2 level chemical/biology laboratory. In addition, the team has added a collaboration with Dr. David Kaplan, Department of Chemical Engineering at Tufts University, to continue development of the phage-displayed ALRs for pathogen detection.

Specific Aim 1: Determination of analytes of interest and detection requirements.

Progress: A coating procedure to apply affinity ligand reagents (ALRs) to the 9-element μCANARY sensor surface using antibodies to microbial pathogens has been developed (Figure 1). ALRs targeted to *enterococci* (blood borne pathogen) detection will be utilized as a proof-of-principle reagent. The coating procedure will be tested on 9-element sensor chips using recently developed individual sensor element addressing techniques with the BioDot™. The procedures involve aminoalkanethiol to activate the sensor surface, followed by the application of glutaraldehyde, avidin, biotinylated anti-human antibodies (IgG), human anti-*enterococci* antibodies, and *enterococci* bacteria. The frequency shifts of the individual μCANARY elements at each layer of coating will be monitored. The optimum concentration and reaction time for each coating material will be determined to achieve the highest degree of binding.

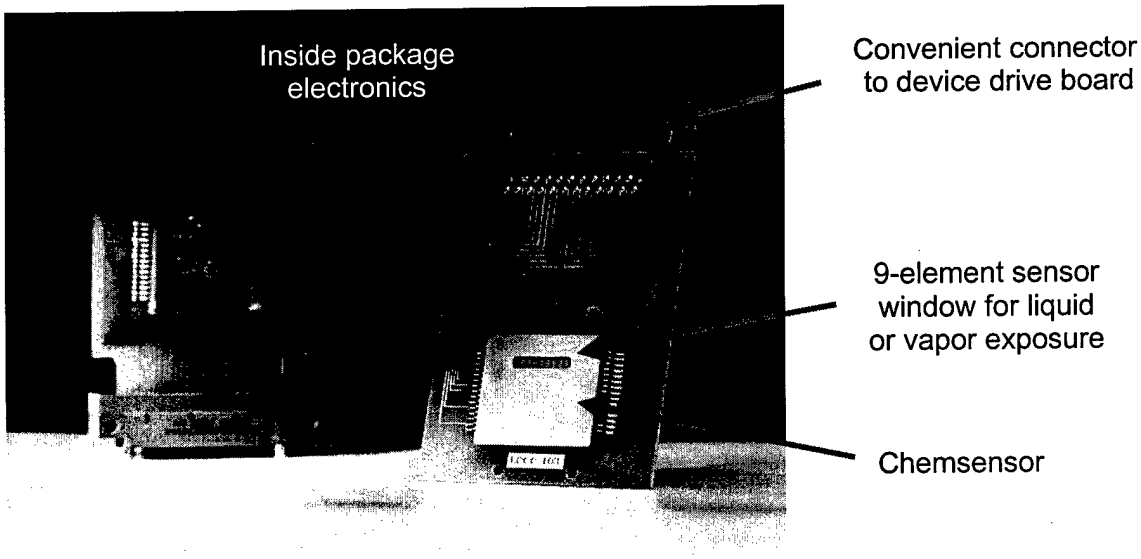


Figure 1. Nine-element μCANARY showing device packaging and device test interface.

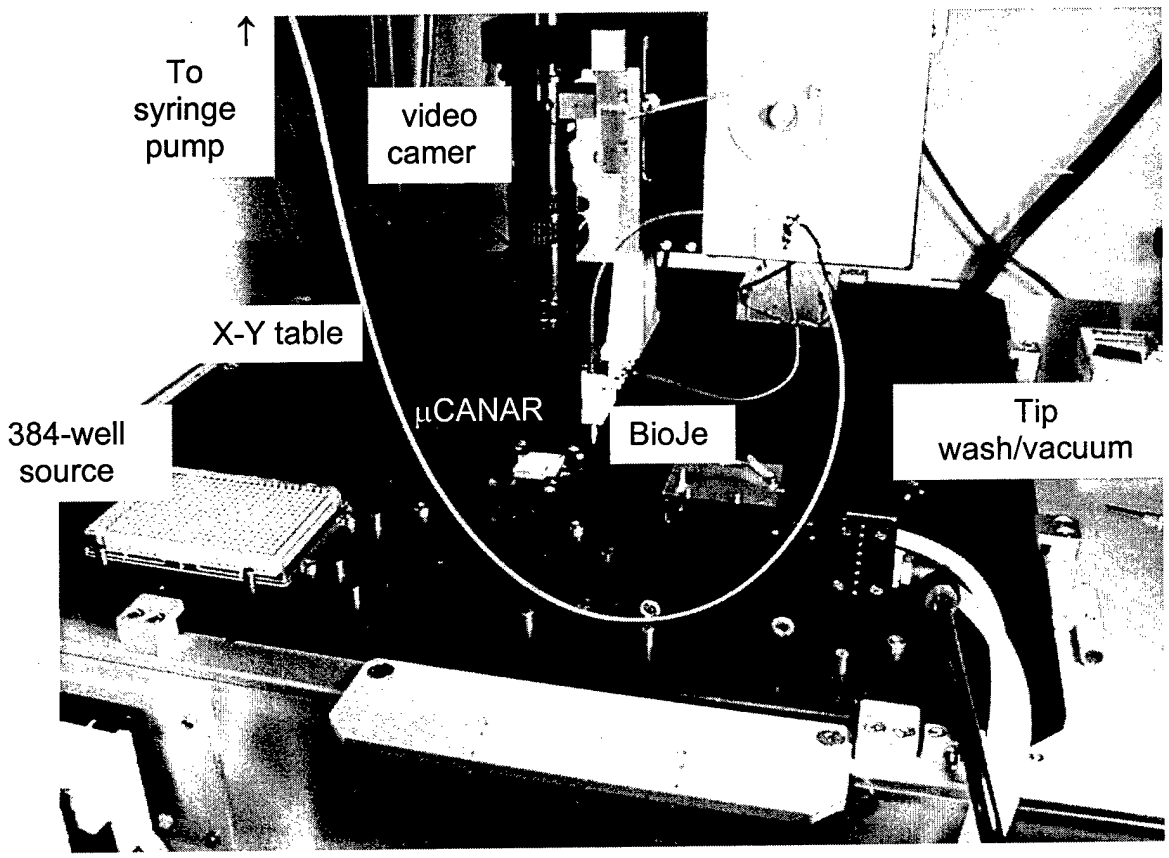


Figure 2. System components of the BioDot ™ apparatus, shown depositing nL amounts of reagents on a 9-element μCANARY sensor.

Specific Aim 2: Develop more sensitive and broader range microsensors.

Progress: Coating procedures to apply ALRs to the μCANARY sensor surface to detect *enterococci* are underway. Our team is developing bioassays for optical identification and detection of pathogens using the BioDot™ to generate arrays on gold-coated microscope slides. Other substrates exhibit either too much nonspecific binding (nitrocellulose) or to little binding (treated plastic, such as NUNC slides). In addition, gold-coated glass slides are still relatively inexpensive and are more relevant to our surface chemistry procedures for the μCANARY sensor. To deposit a very small amount of ALR on the sensor, a BioDotTM apparatus is used (Figure 2).

Analytical studies were conducted to evaluate the precision and reproducibility of the BioDot™ microdispensing technique as the team continues to develop the microorganism assay for both planar substrates and the 9-element μCANARY. Fluorescence microscopy to image fluorescent reagents deposited with the BioDot ™ into the individual elements of the μCANARY sensor (Figure 3) provides semi-quantitative information about coating uniformity across individual sensor membranes as well as between different element

membranes. Good correlation of the frequency response of the devices with the amount of reagent delivered to the elements has been observed in separate experiments.

Fututre Work: Reduce the costs of sensors through improved surface chemistry. Sensor surface chemistry involves the characterization of samples, the determination of the level of accuracy of the sensor technique and the development of hardware and software for the microsensor system. To develop novel surface chemistry and bioassays that can be used for detection of microbial pathogens, nitrocellulose membranes and high affinity plastics, which are simple to use and inexpensive, have been used as the array substrates. These substrates also provide for a larger number of array elements (compared to the 9-element μCANARY currently available), which enables faster screening and optimization of conditions.

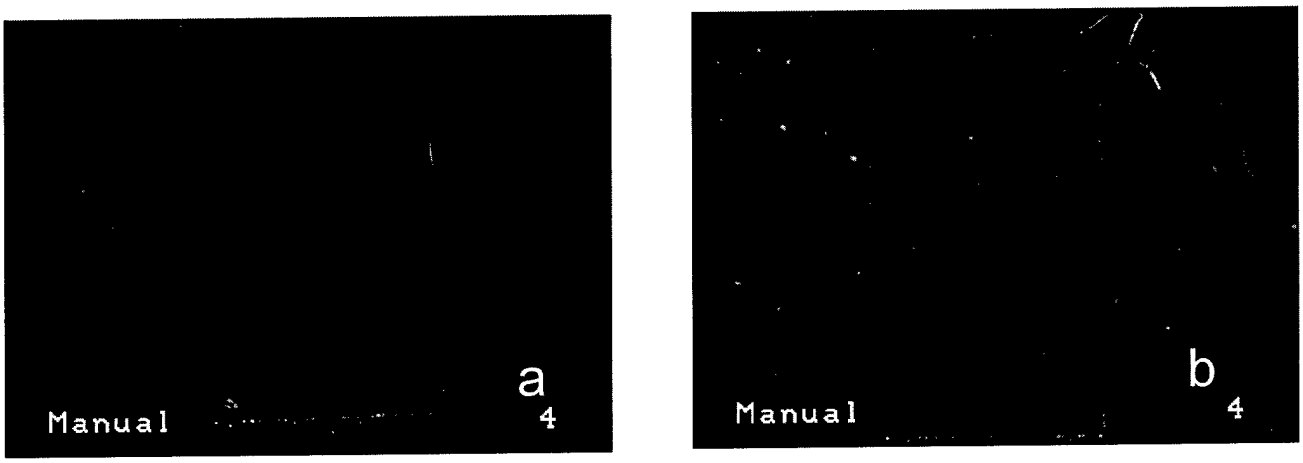


Figure 3. Fluorescence microscopy imaging of reagent deposited into individual elements of the μCANARY with the BioDot. Images are of four different elements of two different 2-element devices illustrating uniformity of deposition: both elements of (a) and both elements of (b) received the same amount of reagent.

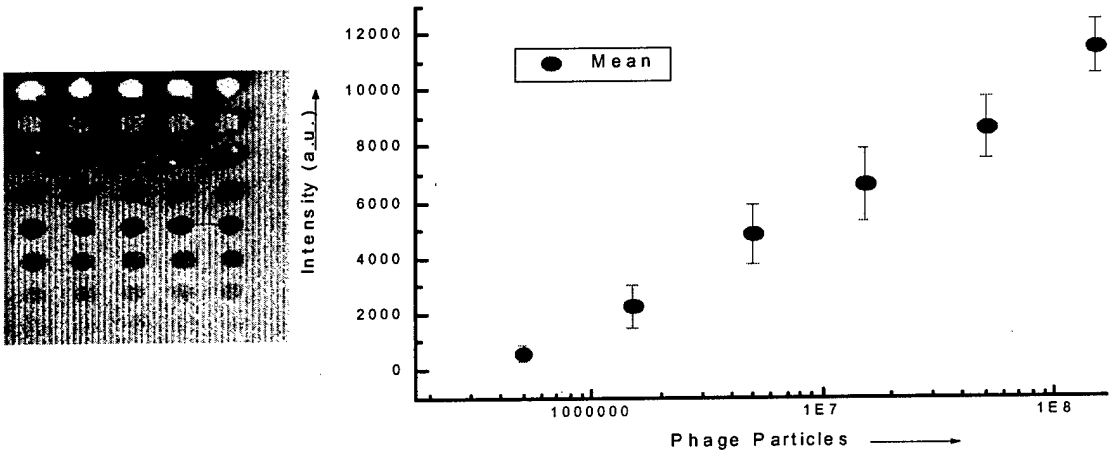


Figure 4. One of the first experiments performed was to microdot an array with 50 nL of *Borrelia burgdorferi* on nitrocellulose blotting paper. This figure shows the results of an experiment using phage as a probe for *Borrelia*. Additional experiments of the types described above are ongoing in an effort to minimize the variance of this technique as the team continues to develop the microorganism assay for both planar substrates and the 9-element μCANARY.

Surface chemistry and bioassay technologies learned from microdot blot experiments on gold-coated glass slides will be transferred and tested on 9-element μCANARY sensors. Experiments using the BioDot™ and a flow cell for immobilization of bioagents will be performed on 9-element sensor arrays. The selectivity and efficiency of using various combinatorial-chemistry tools, including phage library technique, to detect bacteria will be determined. Coating procedure to apply ALRs to the μCANARY sensor surface to detect *enterococci* will be developed. The sensor regeneration method using pH shifts in the solution will be further tested in the *enterococci* detection scheme to determine the number of cycles that the regeneration is effective and the sensitivity change, if any, associated with each cycle.

Specific Aim 3: Determine level of accuracy provided by technique.

Progress: Experiments have been performed to monitor the resonance frequency changes of the sensor when different reagents are deposited on the sensor elements using the BioDot™. While the frequency changes are lower than predicted for the amount of material applied to the sensor, the reproducibility is good. The team is currently trying to verify device response for a given amount of mass loading of the sensor (device sensitivity).

Using the BioDot™ apparatus to microdot arrays on NC substrate, detection limit of ~500 *Borrelia* was achieved, which was ~10 times better than a conventional macro-scale dot blot experiment performed in the same laboratory (result reported in previous report). It is believed that this can be improved by a factor of two-five once the team switches to a high binding substrate that will eliminate nonspecific binding seen with NC. Even greater sensitivity (of the order of 10-20 bacteria) should be achievable with the μCANARY sensor.

Future Work: The linear dose-response curves obtained during sensor evaluation will be used to calibrate the sensors and provide information on analyte concentration. Single- and multiple- component samples with different "known" concentrations, which fall in the LDR of the individual microbes, will be tested on the array μCANARY. The measured and expected concentrations are plotted and analyzed with regression analysis. The correlation will be obtained to determine the accuracy of the measurements. The results will determine whether the technique can be used as a screening tool (i.e. provides only information about the positive or negative presence of an analyte), or as a characterization tool that provides semiquantitative or quantitative information.

Specific Aim 4: Improve the sensitivity of the device through hardware development.

Progress: A significant effort has been made to reduce the noise of the sensor readout to improve the sensitivity of the sensor. In the area of hardware development, devices with different piezoelectric materials and electrode configuration have been fabricated and evaluated to determine the best sensor design that provides the highest signal output. This optimal design used in our fabrication of the twenty 9-element devices (Figure 2) includes a 50:50 sense-to-drive comb finger design with no gap on either ZnO or AlN piezoelectric film. In addition, the electronics on the drive board and within the sensor package have incorporated major changes to provide more stable signal readout while keeping the system compact. In the area of data analysis/software development, the data analysis algorithm has been improved. Previously, only magnitude-frequency spectrum was used to determine the peak frequency. The new algorithm enables the combined use of magnitude and phase information incorporated in a zero crossing discriminant to center resonant frequency. This provides a more accurate determination of the peak frequency reading, the change of which is proportional to mass loading of the sensor. The new algorithm has been successfully implemented in a LabView program, which streamlines the data acquisition and analysis processes on multiple sensing elements on an array. Another major accomplishment is the incorporation of an algorithm to use one of the sensors in a multi-channel device as a reference to compensate for electronic noise, temperature and other effects. This cross correlation algorithm improved stability by a factor of 10 to about 2 ppm RMS (30 minutes) for the 2-element device and to about 20 ppm for the 9-element device. With these improvements, it was determined that the sensitivity of the 9-element μCANARY sensor is approximately 80 picograms. Further reduction in variance with a phase locked oscillator circuit (closed loop) should improve 9-element μCANARY sensitivity to about 0.1 ppm, or about 0.8 picograms. This sensitivity translates into a detection limit of the order of 4 spore particles that have a molecular weight of 1.2×1011.

The team has fabricated 27 sensors that are designed for liquid exposure experiments. The team has achieved near 100% yield in the latest batch of sensor die fabrication using a temperature controlled Oxford system. The first fabrication of devices using the new μCANARY4 mask set has been completed. Eight devices from this batch were packaged in mid-September. The team has tested the 9-element sensor arrays designed for liquid-

exposure and reported observation of good signals. The team is completing data analysis for a full report of device signal intensity, device Q, and device variance of the individual elements of each sensor. Temperature measurement of onboard temperature sensors has now been included on all three drive boards.

The team recently obtained data on the devices with different comb configurations indicated that most devices show similar behavior with regard to frequency spectrum and Q when they are exposed to liquid. Also, as expected, ZnO and AlN give similar performance with better performance than PZT devices. The design uses the standard comb configuration and includes 9-element (44) and 65-element (2) devices in the current fabrication with the μCANARY4 mask set.

Specific Aim 5: Improve the utility and usability of the software.

Progress: An interface has been developed to link the data acquisition software (i.e. LabView) to the data processing program to streamline the data analysis process. A preliminary macro program was written to correct the raw data (i.e. absolute frequency readings) against the reference sensor (common mode subtraction), subtract the results from their baselines, and automatically display sensor frequency shifts.

The team has developed a new data analysis algorithm to combine both magnitude and phase information to obtain a better resolution of the frequency readings. This algorithm, along with the method of using one of the sensors in a multi-channel device as a reference has been successfully implemented into a LabView program. This program now streamlines the data acquisition and analysis of the μCANARY sensor, enabling sequential monitoring of multiple elements of the sensor array continuously (for any specified time frame), and display of a ΔFsensor-ref histogram in real time.

Future work: The team will continue to improve the data acquisition and analysis program to speed up the readout process. Calibration curves and microbial fingerprints of different pathogens will be built into a library that can be recalled to identify the presence and quantities of target pathogen(s). Software interfaces between sample circuit board, analyzer, and computer will be further developed to monitor frequency shifts of the sensor. The current software will be improved to increase the flexibility and speed of controlling the data acquisition and storage processes. Further improvement will be made in the link between the data acquisition software (i.e. LabView) and the data processing program to streamline the data analysis process. A macro program will be written to correct the raw data (i.e. absolute frequency readings) against the reference sensor (common mode subtraction) and automatically display sensor frequency shifts. A database will be built using the dose-response curves (i.e. calibration curves) obtained in measurements. Depending on the results of Specific Aim 3, a program will be written to display the results at the end of a measurement on a PC screen in a simple format, which will indicate the presence or absence of individual microbial pathogens and, if present, the (approximate) concentrations.

3.4 Simulation ATT

The Simulation group has made important progress in the past year. While the overall structure of the research program remains the same, there have been changes in group composition and research goals as outlined below. The team has succeeded in extracting 3-dimensional models of anatomy from medical images as an initial step in creating the dataset necessary for real-time interactions. The team has begun design of a visualization method which can extract fluoroscopic images from cross-sectional data, initially using volume rendered algorithms, and then considering methods based on Fourier Central Slice Theorem, which is computationally more efficient but more difficult to implement initially. The team worked with Dwight Meglan, PhD, of Virtual Presence, Incorporated, on a triaxial haptics interface device which will permit realistic interactions in the simulations, permitting tracking of three separate devices in real time. The design and specifications of this device exceed the available designs from Draper Laboratory and the team will be using this design in our initial procedural simulations. The team has begun tissue-modeling measurements using the TeMPeST-1 device designed during Year 1. These experiments will give us our first actual data concerning *in vivo* small-scale tissue deformations.

The team participated in several important meetings this year, including presentations at SMIT/CIMIT '99, MMVR 2000, SPIE 2000, and a National Library of Medicine Conference on Medical Modeling and Simulation. Dr. Steven Dawson, team leader, took part in the November, 1999 Bushmaster exercises at Camp Bullis, Texas, as part of the group's effort to understand the actual conditions in which combat casualty care is delivered.

The structure of the group changed somewhat as simulation collaborations with Draper Laboratory ended, and new programs were begun with the Harvard University Division of Engineering and Applied Sciences. Discussions began with the Laboratory of Computer Science at the Massachusetts Institute of Technology on a collaborative research program to develop a common modeling language. The team attracted a graduate student who will work on haptics and mechanical engineering efforts under Mark Ottensmeyer, who will be finishing his PhD at MIT this fall and will join the group full time. Recruiting full time committed researchers to the team remains largest unfulfilled goal.

The team has set goals for its first deliverable: a chest tube insertion simulation that will merge mannequin and computer-based simulation into a hybrid trauma training simulation. This procedure was chosen because of the critical role chest wound management plays in lower echelon battlefield care and because of the importance given to this procedure in acute trauma life support (ATLS) training courses used in combat medic training. The team anticipates that this simulation will be ready for initial use in summer 2001.

Specific Aim 1: Tissue Modeling-Develop tools capable of *in vivo* measurement of soft tissue characteristics. A fundamental component in the creation of a simulated environment is the generation of three-dimensional models of the anatomy. Whether the team develops generic simulators or patient-specific simulation systems, the first step toward tissue-tool interaction is the creation of 3D models of the anatomy, in the group's case, vascular structures. Some simulators are based on manually segmented 3D models specifically designed for the purpose of the simulation. The Simulation Group's approach is different since the team plans to create various simulation systems based on the same core of technical components. During Year 1, the team started the development of a segmentation tool. This tool is based on the expertise of team members in the field of medical imaging and relies partially on the VTK software library.

Progress: Successful creation of polygonal surface models of various anatomical structures by applying 3D image processing algorithms on CT data.

Specific Aim 2: Haptics-Enable force feedback of tissue data to render tissue manipulation realistic. Commercially available haptics interfaces have been used principally as an interface for rigid laparoscopic surgery instruments. Devices like the Laparoscopic Impulse Engine® are designed specifically for simulation of laparoscopic procedures and then cannot be used for different categories of procedures. On the other hand, the PHANToM® device is based on a generic design suitable for various applications. It is inherently different in design from actual instruments and requires complex modifications to be used in a natural manner. Also, exchange of a modified haptics device representing one instrument for a different instrument requires significant alteration, even requiring a different interface device. Therefore, new devices will be developed by our group.

Progress: In Year 1, the team pursued a two-part strategy to appropriate haptics interface design. Draper Laboratory created a series of working drafts of single stage interface devices. The team then began design of a multi-stage interface. By focusing on endovascular therapy the team can narrow our haptics interface requirement to flexible tools that interact with soft tissue. Several haptics designs are under consideration, including rolling track and actuator methods to allow 2-degrees of freedom for both the catheters and the guide-wires The eventual device will require coaxial or tri-axial interactivity and the ability to insert and withdraw several different instruments to create a human interface for the user that will be "transparent" and intuitive.

Specific Aim 3: Geometric modeling and visual feedback- recreate on the monitor screen a believable representation of tissue-tool interactions. Effective simulator experience will require graphical realism that permits *suspension of disbelief* for the user. Depending on the procedure targeted by the simulation system, different visual feedback may be required: visible light rendering, ultra-sound images, x-ray images, etc. For the purpose of our primary targets, the team will focus on both visible light and x-ray rendering. Visible light rendering is the most common visual feedback and has been used in previous medical simulations of laparoscopic procedures. Current hardware and software libraries permit relatively easy implementation of visible light visual feedback of

polygonal models, at interactive rates. However the lack of realism in the quality of the rendered images has often been a major criticism for existing simulators, even when using techniques like texture mapping or special light effect. On the other hand, simulation of x-ray images presents the opposite challenge: a simulated x-ray image is more realistic than a simulated endoscopic view of the anatomy but computation times can be long.

Progress: Based upon the software develop for 3D segmentation, the team added a volume rendering algorithm. This algorithm produces images that are very close to x-ray images. The major drawback of this method is its very high computation requirements, which do not yet allow real-time interaction with the simulated x-ray images. Real-time rendering of surface under visible light can be done very efficiently by current 3D graphics boards, assuming the number of polygons remains moderate. Therefore, a decimation algorithm has to be applied on the mesh created by the segmentation process to reduce the number of triangles used to describe the surface of the model.

Specific Aim 4: To develop a common anatomic modeling language to achieve integration of physiology into computerized representations. The pursuit of a Common Anatomic Modeling Language (CAML) is the keystone of the development of Simulation Program, and it may become an essential element in the establishment of collaboration with other medical simulation groups. A schematic representation of CAML is shown below (Figure1).

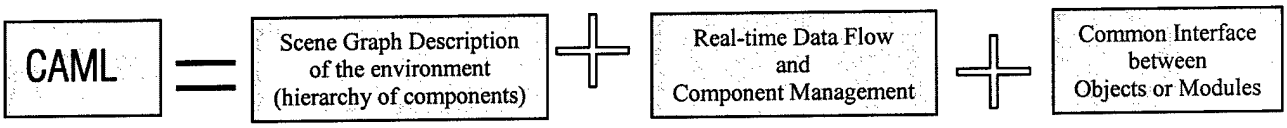


Figure 1. Conceptual design of CAML.

Progress: The team has begun discussions with the Laboratory of Computer Science (LCS) at the Massachusetts Institute of Technology, Dr. John Guttag, head of Electrical Engineering and Computer Science at MIT and director of the LCS, sees the design of CAML as a "decade vision" and a decade-long commitment. He has recommended that our group form a relationship with the software design team at LCS, led by Drs. Daniel Jackson and John Chapin. A conceptual description of CAML was described in a conference paper at the 2000 SPIE conference in Orlando.

Specific Aim 5: Demonstrate a hybrid chest tube simulation system. At ATACCC in September, 2001. The team chose a chest tube insertion simulator as one of its early demonstration projects. Chest tube insertion is a frequently performed procedure in acute combat casualty care management from Battalion Aid Stations through rear echelon medical centers. Insertion and management of these tubes is one of four surgical skills taught in the Advanced Trauma Life Support course (chest tube insertion, pericardiocentesis, surgical airway and diagnostic peritoneal lavage).

Progress: The design the team has outlined will incorporate both mannequin-based and computer-based simulations into one training module. The design specifications are intended to provide a durable, simple, effective system capable of training 50 high school educated trainees in one morning.

The team has had discussions with a Naval Trauma Surgeon (Peter Rhee, MD) and a member of the 375th Ranger Special Operations Forces (Sgt Bob Miller) to define the mandatory components for chest tube insertion as practiced in those two settings. The "final" concept of the system has been defined, consisting of a computer-controlled mannequin (torso), a monitor, a chest tube equipped with position sensors and a software control and display system. The simulator will allow a trainee to perform tube placement for hemothorax, pneumothorax, and tension pneumothorax.

3.5 Tissue Engineering

The Tissue Engineering Program is establishing a platform technology to meet the overall goal of dramatically improving patient care. The specific targets can be applied to the care of the wounded soldier by alleviating the organ shortage, compensating for massive tissue defects, and creating optimized living replacement structures for

- Structural tissue repair including bone, cartilage, and muscle.
- Cardiovascular repair including blood vessel substitutes, heart valve substitutes, and cardiac muscle replacement.
- Neural repair including spinal cord and peripheral nerve.

The CIMIT Tissue Engineering Program is a focused, multi-disciplinary, multi-institutional effort to discover, demonstrate, and develop a revolutionary new technology that will enable a safe, reliable and reproducible national supply of replacement vital tissue, including entire organs. During its first two years, the Tissue Engineering effort has met or exceeded every milestone, established and maintained a fiscally responsible, organized, nationally and internationally recognized laboratory, and has successfully recruited top graduate, post-doctoral and faculty researchers from leading research centers around the world. CIMIT has also established an active and strong research program with MIT. With CIMIT support, Dr. Robert Langer is directing the development of two new classes of innovative biomaterials that show great promise for independent breakthrough medical applications in gene therapy and medical implants, as well as dramatic potential for advanced substrates for future tissue engineering applications. Many Tissue Engineering projects involve close collaboration with the Draper Laboratories.

The world crisis in the availability of donor organs to replace failed organs in critical patients of all ages is well known, and the particular needs of the wounded soldier are manifest. Some progress has been made; hospitals are now using limited amounts of skin, ligament, cartilage and even bone produced by tissue engineering methods.

While these successes are encouraging, the ultimate goal of "off the shelf" organ replacements remains elusive. Liver, pancreas, kidney, and even neural tissue have now been shown to be supportable and to function to a limited extent on synthetic substrates, membranes, and micro-fibers. However, the lack of an adequate and hemodynamically correct blood supply for these differentiated cells has so far blocked the production of organs at practical volumes.

This program addresses the general problem of supplying sufficient blood supply to an engineered solid organ through the use of a universal tissue-engineered capillary system that can be specialized by the addition of organ-specific differentiated cells. During the first two years of the Program, several key steps essential for the production of a tissue-engineered vascular system have been demonstrated.

The overall goal is to develop tissue-engineered devices composed of living cells on matrices which, upon implantation, are vascularized either *in vitro* or *in vivo*. The major project related to this goal is to synthesize vascularized systems from the platform of 2-D silicon microfabrication technologies and adapt to three-dimensional living devices. Much progress toward proof of principle involved in this approach has been achieved over the last twelve months. Progress can be divided into; a) design of systems, b) microfabrication of devices, c) testing of devices *in vitro*.

Over the past year, a design team of engineers has been built under the supervision of Dr. Roger Kamm, Director of Mechanical Engineering at MIT, and Dr. Jeff Borenstein, Director of microfabrication at Draper Laboratories. A post-doctoral fellow involved in the optimization of microvascular channels for organ fabrication including topology design and hemodynamic and transport modeling has been hired. Also, the team has two students, a Ph.D. candidate in mechanical engineering at MIT, and a Harvard Science and Technology (HST) student involved in design. Four major goals have been identified for the project:

- Development of a mathematical algorithm for the design of the topology of Microvascular networks,
- Modeling and simulation of blood rheology and flow in microvascular networks,
- Modeling and simulation of mass transport processes for oxygen and nutrients in the microvascular network and surrounding tissue, and
- Execution of a parametric study to optimize the pattern of the microvascular network.

The continuing research plan is to develop a tissue-engineered device *in-vitro* composed of living cells and matrix with its own branching vascular supply which, upon implantation into animals, would allow immediate perfusion to all of the living cellular elements, thereby forming a new vascularized living tissue.

Task 1: Synthesize vascularized living systems from the platform of 2-dimensional silicon microfabrication technologies and adapt to 3-dimensional living devices

Specific Aim 1: Design and fabricate silicon and Pyrex based systems providing an array of etched channels to act as a mold for generating a living network in two dimensions. In particular:

- Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold.
- Design bioreactors to house the device during tissue formation and folding.
- Develop assays to study the generation of tissue and its histologic, biomechanical, and biochemical parameters.
- Investigate mechanisms of tissue development using molecular markers for gene developmental programs and programs of wound healing and regeneration.
- Begin animal implantation studies to begin to understand perfusion, survival, and function of the living device.

Progress:

Design, fabricate and test systems:

Endothelial cells (ECs) harvested from rat lung's artery have been successfully seeded and expanded under continuous flow condition in the vascular branching network pattern channels etched on a Pyrex or silicon wafer, which was reported before. (See Figure 3) Etched Pyrex or silicon wafer was sealed with silicone rubber to a piece of flat Pyrex of the same size and assembled in a bioreactor system with low pulsatile flow pump. Using a variable flow pump, 4.3 x 10^4/ml ECs in medium was loaded overnight. ECs were observed flowing through channels and attaching mainly around the walls of smallest channels (15 μm width and 20 μm depth) on DAY 1 and growing to confluence along the channels under continuous flow condition over the following 5 days. After verifying the patience of this system by using fluorescent micro beads (0.5 μm), red blood cells (approximately 5 m), harvested from rat were heparinized and then perfused into these endothelialized channels with the pump system, and successfully collected at the output.

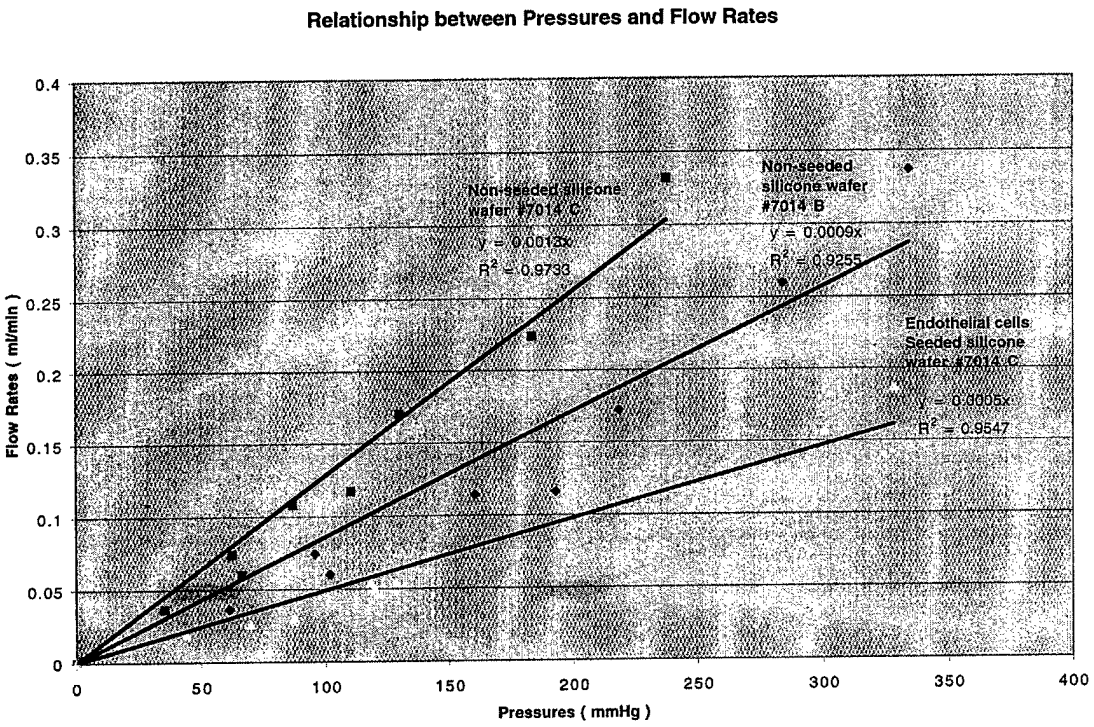
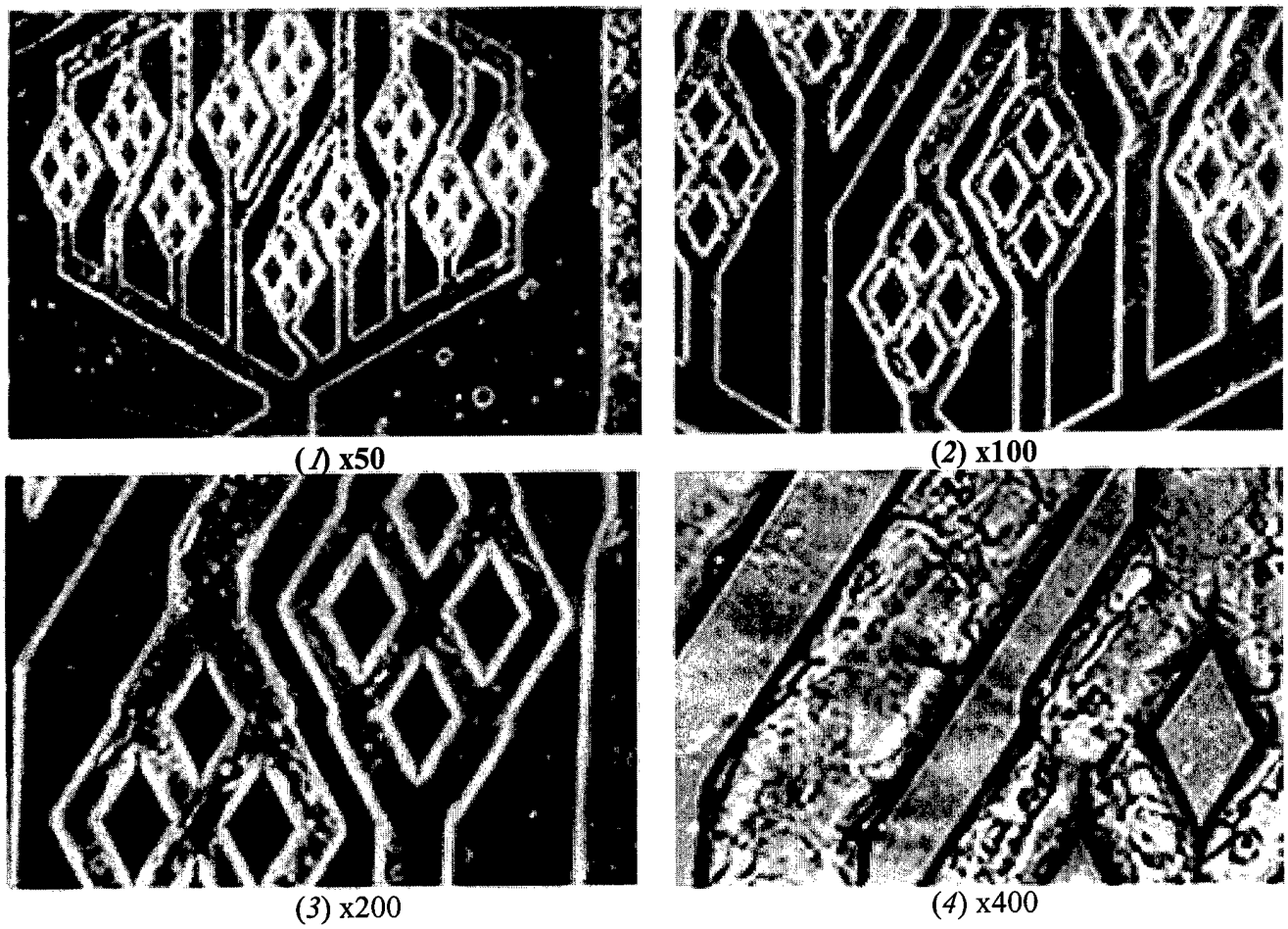


Figure 1. This graph shows relationship between pressures and flow rates in the entire branching channel network on the silicon wafers (15 μm width and 40 μm depth). They were sealed with silicone rubber in specially designed bioreactor system and measured parameters using a variable flow rate pump.

Figure 2. Food color dyed water was flushed through branched channels constructed in biodegradable polymer sheets. Only perfused channels were seen as yellow pathways because biodegradable polymer sheets were translucent.



(*1*) x50 (*2*) x100

(*3*) x200 (*4*) x400

Figure 3. These pictures show the attachment and growth of endothelial cells along the etched channel network on Pyrex under continuous flow conditions. Magnifications of x50 (*1*), x100 (*2*), x200 (*3*), x400 (*4*) pictures are shown respectively from the upper left to lower right. Each individual nuclei of Endothelial cell can be recognized in highest magnification.

Three dimensional culture system:

Progress: In our current three dimensional culture system under flow condition, the team succeeded in culturing a mixture of rat small hepatocytes, which are known as "committed progenitor cells", and non-parenchymal cells with creating new tissues including ductular structure on the three dimensional PGA polymers. These new tissues maintained the high level of albumin production up to 3 weeks as measured by ELISA. These results indicate that this bioreactor can be used as a very useful assay system for tissue engineered small pieces of liver.

Two dimensional to three dimensional tissue:

Progress: Last year, the team demonstrated the growth and proliferation of hepatocyte sheet implanted onto rat omentum under hepatotrophic stimulation with retrorsine treatment, PC shunt, and hepatectomy. A two dimensional cell sheet was formed into a three dimensional tissue by rolling it up with omentum. Histology of similar experiment using cell sheet of small hepatocytes and non-parenchymal cells showed attached

hepatocytes and ductular structures composed of two cell types which might suggest the transition of one cell type to another cell type.

Hepatocyte stem cells:

Progress: The team is currently collaborating with two laboratories which are researching liver stem cells. One is Dr. Mulligun's Lab in Children Hospital, Boston, MA working on sorting of the Hoechst-stained side population (SP) cells, which was originally developed as one method for purifying hematopoietic stem cells. They found that liver also has SP cells fraction, which might be the stem cells of the liver. The team is currently sorting SP cells from murine liver and has found they are rich in a non-parenchymal fraction of cell suspension after low g centrifugation. The other laboratory is Dr. Griffith's group in MIT. They have derived several rat liver epithelial cell lines by limiting dilution cloning of cells from the supernatant fraction of low g sedimented cells from collagenase-perfused rat livers. Some of them show strong albumin expression under reduced serum condition. This past year, the team has developed the *in vivo* model to evaluate the differentiation of these cells into hepatocytes. Briefly, these cells are seeded on silicon wafer and lift up from silicon wafer as a complete sheet. The sheet is implanted onto rat omentum under some hepatotorophic stimulations.

Other collaborations and research:

The team has establishing a collaboration with the Harvard Center for Genomic Research to begin studies of gene expression comparing normal hepatic development with normal hepatic regeneration and tissue engineered liver development. Progress in novel degradable polymer constructs to be used in these experiments has continued under the direction of Dr. Cathryn Sundback.

Task 2: Synthesize vascularized living systems from the platform of three dimensional printing technology

A mathematical algorithm has been designed based on a fractal branching model, which allows for asymmetric branching structure and is equipped with a non-intersection rule. A computational algorithm was designed for simulation of blood flow in microvascular networks, taking into account blood rheology and two-phase composition, strong dependence of blood viscosity and network resistance on hematocrit and vessel diameter, and red cell distribution at bifurcations. Work is in progress to simulate the transport processes of oxygen and nutrients in the microvascular network and in extravascular regions. An algorithm has been designed and the computer program is being developed in which governing partial differential equations are discretized across the whole microvascular network domain using finite element techniques.

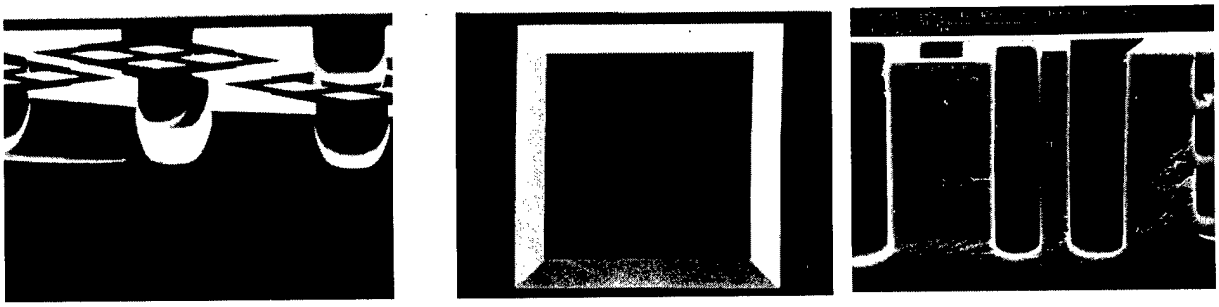
Specific Aims:

- Optimize the design of 3-D polymer systems with an internal tubular branching architecture based on the flow and pressure dynamics of rat liver and rat skeletal muscle.

- Optimize the design and fabricate *in vitro* flow bioreactors to generate vascularized liver and skeletal tissue, which permit their analysis. Develop assays to study the generation of tissue and its histologic, biomechanical, and biochemical parameters.
- Investigate mechanisms of tissue development using molecular markers for genetic developmental programs and programs of wound healing and regeneration.
- Begin animal implantation studies to begin to understand perfusion, survival, and function of the living device

Progress: The team has made considerable progress in wafer-level channel network design as well as in the fundamental micromachining technology for mold fabrication. In Year 2 a second prototype design was added to micromachined wafers to more closely replicate physiologic fluid flow conditions and to provide equal pressure drops across each path in the network. In addition to the second prototype, two other designs have been generated and fabrication has begun. The first design is aimed at investigations of the capillary-hepatocyte interface, and is comprised of two channels in close proximity separated by a semipermeable membrane. A second design involves Draper Laboratories growing technology in the area of microfluidics. A set of model networks specifically designed to investigate fluid dynamics in capillary-size micronetworks has been produced, and fabrication of flow chambers based on these designs has been initiated.

Also, significant improvements in basic micromachining technology were made. Research during Year 1 demonstrated that channel etch profiles have a dramatic effect on cell attachment, adhesion and confluence. In Year 2, three etch techniques were explored and a baseline isotropic plasma etch process was selected and optimized. Profiles comparing straight sidewalls with a semi-circular profile and with an angled sidewall have been generated. Experiments have demonstrated the semi-circular profile produced the best tissue and the microfabrication process was further optimized to enhance sidewall smoothness and eliminate notching at the surface. During the second year both positive molds of channels as well as negative molds were produced. The negative mold technology utilizes a photolithographic process called "image reversal", in which the same photomasks are used to produce inverse channel geometries by reversing the polarity of the lithography process. From this negative mold, imprinting techniques as well as polymer techniques can be used to directly transfer the positive pattern into degradable polymer systems.



(a) Isotropic Curved Wall etch, (b) Angled Side Walls, (c) Straight Wall Plasma Etch

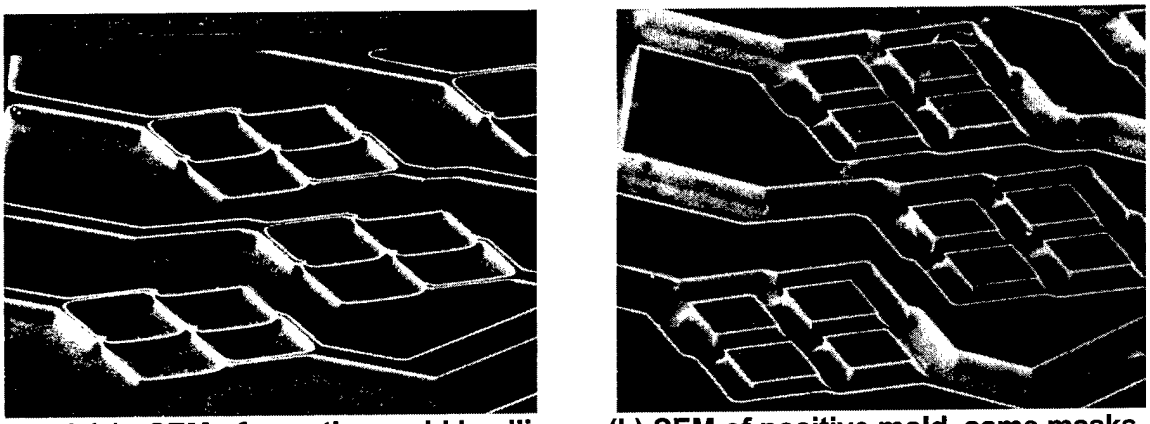


Fig. 2 (a). SEM of negative mold in silicon. (b) SEM of positive mold, same masks

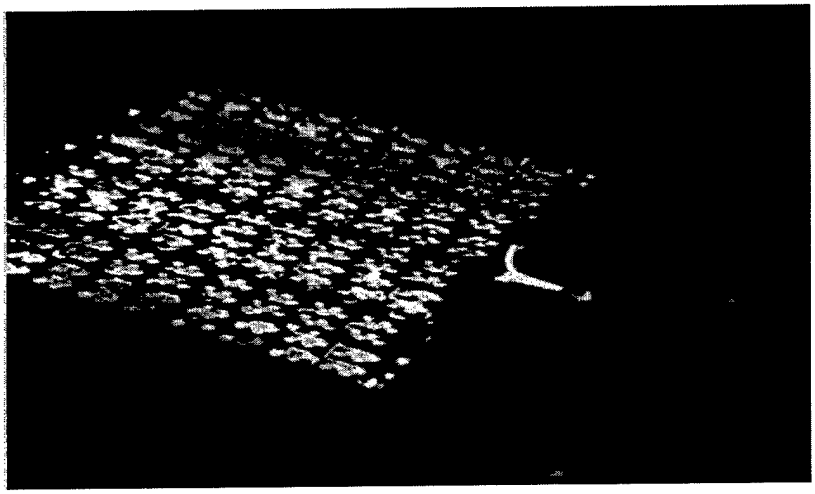


Figure 3. Microfluidic study of micromachined channels in silicon using fluorescent dye flow

The relationship between pressure and flow rate of the liquid traveling through microfabricated vascular branching network channels etched on the wafers has been revealed by measuring the input pressure and the volume of output flow in a sealed bioreactor system. Then this was examined under conditions with or without endothelial cells that were seeded under static conditions before assembling bioreactor. In both cases, they showed a linear relationship between pressure and flow rate. Higher resistance was seen in the seeded channels.

Hence, the team could conclude that regardless of the complicated patterns or number of channels, the flow through the branching network obeyed Ohm's law overall.

Microfabrication on polymers:

Progress: Vascular channel network patterns with a minimum 15mm width and maximum 40 m depth, which were designed and reported before, have been successfully replicated with a biodegradable polymer (poly- (DL-lactic-co-glycolic acid)) sheet, approximately 100 μm thick, using negative etched silicon wafers or etched

silicone elastomer molds. The etched polymer sheet was peeled from a mold without destroying its channel structure because the physical properties of the two materials led to different amounts of contraction at -195 degrees Celsius. This cast polymer sheet was attached to a flat, biodegradable polymer sheet of the same size and sealed by evaporating the residual chloroform in the polymer at room temperature. Then water was flushed through the channels with a syringe, which demonstrated patience almost entirely through some channel pathways, as there was minor leakage. This outcome indicates the potential for these sheets to be used as a biodegradable scaffold for vascularized living system, see Figure 2.

Task 3: Minimally invasive meniscal repair with tissue engineered cartilage.

The central hypothesis of this project is that a lesion in the meniscus can be repaired using isolated autologous chondrocytes or, other cell population stimulated to chondrogeneic differentiation, and seeded onto a bioresorbable scaffold. The scaffold could be allogeneic devitalized meniscal tissue or other synthetic materials to be investigated. The cell-seeded construct would be then interposed in the meniscal lesion and secured in place. Healing would be achieved by the bonding capabilities of the cells. The goal of this section will be to develop and refine the model for creating a reproducible meniscal injury in the medial meniscus of miniature swine. Once this goal is achieved, new constructs or variables to be tested in subsequent stages of the project will be tested in the same fashion for consistency.

Specific Aim 1: To demonstrate that chondrocytes, seeded onto a matrix scaffold, can be used as valid therapeutic approach to achieve a secure meniscus repair in a preclinical orthotopic model.

Progress: To date, seventeen pigs have been operated in which a bucket-handle lesion has been made in the medial meniscus of the left knee (Table 1). In the five animals in group A, the lesion has been treated with a scaffold seeded with articular chondrocytes and secured into the lesion with a suture. In the four animals in control group B, the lesion has been treated with the scaffold without seeded cells and secured with a suture. Four animals in control group C have had the lesion treated with the simple suture. The lesion has been left untreated in four animals in control group D.

Pig #	Date 1st surgery	Side	Date 2nd surgery	Lesion/Treatment	Follow-up	Date Sacrifice	General Results
18	1/5/00	L	--	Suture only	9 weeks	3/8/00	Not repaired
19	1/5/00	L	--	Scaffold w/o cells	9 weeks	3/8/00	Not repaired
20	1/18/00	L	2/9/00	Exp: scaffold w/cells	9 weeks	4/12/00	Weak repair; chip in site
21	2/8/00	L	2/24/00	Exp: scaffold w/cells	9 weeks	4/24/00	Weak repair; chip in site
22	2/8/00	L	2/24/00	Exp: scaffold w/cells	9 weeks	4/24/00	Weak repair; chip in site
644	6/6/00	L	--	Scaffold w/o cells	9 weeks	8/8/00	Not repaired
643	6/6/00	L	--	Untreated	9 weeks	8/8/00	Not repaired
23	7/6/00	L	--	Suture only			
24	7/6/00	L	--	Untreated			
656	7/13/00	L	--	Scaffold w/o cells			
657	7/13/00	L	--	Suture only			
658	7/13/00	L	--	Suture only			
659	7/13/00	L	--	Untreated			
660	7/18/00	L	8/3/00	Exp: scaffold w/cells			
661	7/18/00	L	8/1/00	Exp: scaffold w/cells			
662	7/21/00	L		Untreated			
663	7/21/00	L		Scaffold w/o cells			

Table 1

Seven pigs have reached the 9-week time point of follow-up and have been sacrificed. The lesions have been evaluated grossly and specimens submitted for histological processing. Of those, three were from the experimental group A, two from the control group B, one from the control group C, and one from control group D. The remaining animals are completing the scheduled follow-up.

Gross evaluation showed bonding of lesion margins in the specimens from group A where the scaffold was still present in the lesion site (Figure 1A). Macroscopic analysis of the control specimens indicated the presence of not repaired lesions (Figure 1B). In the animals from group B treated with the devitalized chip without cells, the chip was not found at the time of necropsy.

Histological analysis showed complete adherence between the margins of meniscal fracture and the cell-seeded scaffold in several areas in the specimens of group A menisci (Figure 1C); the arrows in the picture 1C represent the limit between the scaffold (left) and the outer part of the meniscus. Other areas of the same specimens showed interruption of continuity between the seeded scaffold and the native meniscus lesion edges. Where repair was achieved, newly formed cartilage matrix was involved in the bonding process. On the other hand, no matrix formation nor signs of repair was seen in the specimens of all control groups (Figure 1D).

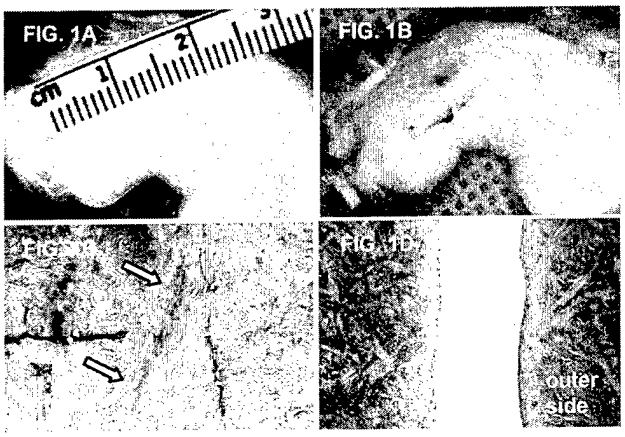


Figure 1. (1A) Gross evaluation of group A, (1B) macroscopic analysis of control specimens, (1C) histological analysis of group A, and (1D) neither matrix formation nor signs of repair were seen in the specimens of all control groups.

Future Work: Investigate other cell sources and different absorbable materials for cell scaffolding to accomplish a minimally invasive meniscus repair technique.

Although autologous chondrocytes may serve as the 'gold standard' for assessing the repair ability in the early phases of these studies, the morbidity associated with harvesting articular chondrocytes from uninvolved joints may preclude clinical application of these techniques. Alternate sources of cells may be adequate or even preferred over the use of articular chondrocytes. Studies on cell source will include articular cartilage chondrocytes, having already been investigated in our previous studies. Dermal fibroblasts or bone marrow stem cells could be also used. The latter two cell sources would require chondrogenic differentiation, possibly by using induction growth factors. Each of these cell sources will need to be explored in the nude mouse model prior to orthotopic repair in the swine model.

The scaffold employed in the pilot study was meniscal tissue, devitalized through freezing/thawing cycles. However, this method presents technical problems in a clinical setting. If autologous tissue is considered, availability of suitable scaffold would be the limiting factor. If allogeneic meniscus is employed, issues related to safety of the implant must be considered, although the team does not exclude the possibility to use an allogeneic meniscal matrix scaffold also in human therapy. Synthetic bioresorbable

materials could be more desirable. The goal of this section will be to test new scaffold materials.

Cell sources to be tested:

- Articular chondrocytes
- Dermal fibroblasts
- Bone marrow stem cells

Possible Scaffolds:

- Polyglycolic acid felt
- Resorbable foams
- Mixed biological/synthetic materials

Progress: This second aim has been investigated *in vitro* thus far.

Cell sources:

Articular chondrocytes have been employed in the orthotopic model under Specific Aim 1. The results have demonstrated that bonding can be achieved using articular chondrocytes. The significant morbidity associated with harvesting articular chondrocytes, however, makes this an unlikely cell source for clinical application.

Bone marrow cells have been isolated from the pig tibia bone marrow. Dermal fibroblasts have been isolated from pig skin. Both types of cells have been grown in monolayer culture to confluence. Studies are now underway to test these cell sources for their ability to form bonds in meniscal tissues in the nude mouse model.

Scaffolds:

Vicryl® meshes in two preparations "knitted" and "woven" have been studied as potential scaffolds for cell delivery. Articular chondrocytes have been shown to be able to adhere to the scaffold material and grow over the culture time (Figure2).

Figure 2. Articular chondrocytes grow among the Vicryl® meshes in a circumferential distribution.

4.0 TECHNOLOGY ASSESSMENT AND OUTCOMES ANALYSIS PROGRAM

The Technology Assessment and Outcomes Analysis Program was established to facilitate accurate and expeditious evaluation of new, minimally invasive technologies. Our goal was to develop a program fully integrated with all CIMIT research, clinical, education, and administrative activities. The Program's principal activities include decision analysis (DA), cost-effectiveness analysis (CEA), outcome analysis and other policy-relevant research. These are carried out to help CIMIT accomplish the following:

Specific Aims: To focus resource allocation for the development of new minimally invasive technologies, to facilitate rapid and accurate assessment of effectiveness and cost-effectiveness, and to demonstrate the value of these technologies to the public, physicians, payers, industry, and legislators to facilitate appropriate implementation.

Progress: The Program now includes 11 individuals (partially funded through CIMIT) with training and expertise in the core disciplines of biostatistics, epidemiology, economics, decision science, outcomes analysis and health care policy. Program activities are well integrated with all CIMIT initiatives, and Program members participate in the full spectrum of CIMIT research, clinical, educational, and administrative activities. Key interactions are summarized below.

Stroke:
Working with the Stroke Program, the team developed a database with over 7000 patients treated for cerebrovascular disease at MGH or BWH during FY 94-99. This database provides the capability to answer questions concerning the costs and benefits of stroke treatment and will enable analysis of diagnostic and therapeutic interventions. An economic model was developed to predict stroke costs and outcomes, and investigate the benefits of early triage (based on diagnostic testing), as well as the role of comorbidities and socioeconomic status in determining outcomes. A manuscript comparing the costs of acute ischemic stroke, across different stroke subtypes, is under review (Medical Care). A grant application has been submitted (AHRQ) to secure funding for further investigation regarding the role of functional CT in acute ischemic stroke. Work is also continuing on a formal CEA of intra-arterial thrombolysis. An analysis of functional neuro-imaging has recently been initiated.

Image-guided therapy:
The team has investigated the cost-effectiveness of surgical resection of liver metastases from colorectal carcinoma, and the effect of diagnostic imaging in this setting. Several manuscripts based on this work are in the final stages of preparation. The team is in the process of expanding this analysis to investigate the benefits and appropriate role of image-guided, *in situ* tumor ablation.

The team worked with Dr. Norman Nishioka to design and implement an analysis of the appropriate role and potential benefits of OCT in upper gastrointestinal disorders, and ALA-assisted endoscopy in Barrett's esophageal dysplasia. The study is ongoing.

A cost-effectiveness analysis (CEA) of imaging and therapy in patients with pancreatic cancer is nearing completion. A complex decision analytic simulation model was developed and verified by comparing its predictions to actual clinical data. The results of this study will be ready for publication soon.

Simulation:
An analysis of medical simulation has recently been initiated. This involves an investigation of learning curve dynamics and their relationship to medical errors and training costs. Due to the lack of significant prior work in this field, the research is largely theoretical. However, progress has been rapid and the analysis has begun to establish a basis for determining the impact and value of medical simulation as a training tool in a variety of clinical settings.

Catheter-based interventions:
A cost-effectiveness analysis of percutaneous abdominal aortic stent placement is underway. This involves a comparison of percutaneous stent placement to open surgery, and an assessment of the impact of this new technology on patient survival and costs, as well as the population-wide effects of changing treatment thresholds. A manuscript comparing the cost of open surgical and endovascular repair has recently been accepted for publication; a related paper is under review.

Menorrhagia:
An assessment of quality of life in patients with menorrhagia is underway. The goals of this project are to assess health-related quality of life preferences, to further refine a new assessment instrument (the "binary gamble" method; initially developed by Johanna Bosch for use in peripheral vascular disease) and develop a decision model to evaluate the cost-effectiveness of minimally invasive therapies (e.g., uterine artery embolization).

Substantial progress has been made developing collaborations throughout CIMIT. Technology Assessment and Outcomes Analysis Program members have provided consultative services to the entire family of CIMIT investigators, including guidance and support on such issues as project feasibility, study design, optimal endpoint determination, and approaches to data analysis. The team has also assisted with the collection and analysis of project data.

Future Work: The team has succeeded in assembling a large and capable group of investigators, and has begun to develop funding sources for the group from outside of CIMIT. The Program is solidly established and positioned to be a major part of CIMIT in the future. For the upcoming year, goals are:

- To continue to support and provide consultation to the full spectrum of CIMIT activities.
- To develop more substantive collaborations with additional CIMIT investigators.

- To work closely with the new Operations Committee and Office of Technology Development to identify and focus on programs with the highest potential impact.
- To continue the team's joint and collaborative efforts with Dr. John Smith and the Regulatory Affairs Program.
- To focus on select major CIMIT initiatives (National Stroke, Vulnerable Plaque, Image-Guided Therapy, Catheter-Based Interventions and OR of the Future).

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5.0 Core Activities

5.1 Education

The Education Program was established to develop innovative methods of training and education in technology-based and interdisciplinary medical research and practice. The intent was to develop a program that would create novel approaches to training and education, integrated with all of CIMIT's research and clinical activities. The Program's principal activities in the past year included the development of simulation-based training tools, oversight of CIMIT's internal education Forum, and the integration of students into CIMIT's research activities. In the future, aspects of the Education Program devoted to the Simulation Program and the Surgical Planning Laboratory will be directly incorporated into these programs. Forum activities will continue as before, with greater emphasis on technology directed to medical care, to reflect a heightened interest in creating more technology/medical interactions.

The CIMIT Forum CIMIT has established a weekly 2 hour Forum in which approximately 75 people from multiple disciplines and institutions come together to discuss a topic related to the application of technology to medicine. It is in this Forum that the role of CIMIT as a catalyst for the application of technology to healthcare is most visible. The focus is to bring together scientists and engineers working at the frontiers of high technology with clinicians who are at the forefront of medicine. The Forum is a vital tool for creating these collaborations, leading to new devices and procedures that will be used to the benefit of patients.

Speakers are invited from around the world and from the rich research milieu of our local institutions, chosen for their pioneering work on new procedures, new applications, or new technologies. The format is designed to stimulate discussion and the interchange of ideas. The talks are short (20-30 minutes) with adequate time for questions. Discussants who are expert in the speakers' field are invited to probe and help the audience draw out the speakers and help stimulate understanding and new ideas.

Each CIMIT Forum includes two presentations with time between the presentations for informal discussion. It is from these conversations that many of our more successful collaborations have sprung.

Other Education Program Goals:

Goal: Develop leading edge technology-based systems for medical training.

Progress: In the past year, the Education Program has assisted the CIMIT Simulation Program to define a specific procedure and to refine technical requirements for the haptics and modeling components of its first simulation-trainer prototype. The Education

Program has collaborated with the CIMIT Simulation Program and CIMIT Surgical Planning Lab to apply for funding as an NIH Bioengineering Research Program, which includes development of a second prototype system in conjunction with the CIMIT Surgical Planning Lab. The Education Program has collaborated with the Center for Medical Simulation to design and begin execution of a study to develop and validate assessment tools and training curriculum for cardio-pulmonology. A partnership with the PASTUER program in patient-oriented research was set up to produce curriculum and experiments in simulation-based education in conjunction with the CIMIT Education Program and the Center for Medical Simulation.

Goal: Engage students in CIMIT research on a regular and formal basis.

Progress: The Education Program has initiated collaborations with the Health Sciences and Technology (HST) program at the Massachusetts Institute of Technology (MIT) and Harvard Medical School to integrate students from HST into CIMIT research activities, including a series of information sessions about CIMIT for HST students in the spring as part of the HST curriculum. Also, CIMIT faculty served as mentors for the PASTEUR program in patient oriented research, working with selected medical students from Harvard Medical School (HMS) on projects in transnational research. CIMIT research projects also routinely employ graduate students and fellows as part of their work (see list following).

5.2 Regulatory Affairs Initiative

Timely Food and Drug Administration (FDA) marketing approval and third-party payer coverage/reimbursement is crucial to achieving maximum clinical impact of new medical technologies. The Regulatory Affairs Initiative at CIMIT has established a unique resource to address regulatory and coverage/reimbursement challenges that arise during product development and beyond.

During Year 2, the Regulatory Affairs Initiative has made significant contributions to policy development through scholarly analysis of 'least burdensome means' under the Food and Drug Administration Modernization Act of 1997 and Health Care Financing Administration (HCFA) coverage and reimbursement policy, and subsequent substantive discussions with government and industry. A web-based 'least burdensome means' decision tree is in the early stages of development in concert with FDA and industry, while potential CIMIT-HCFA collaborations are being explored. These and other projects are designed to make marketing and coverage/reimbursement decisions more transparent and reproducible, with the concomitant effect of moving new technologies into clinical practice sooner, thus ensuring maximum impact on patient care.

Progress Toward Goals:

Goal: Maintain an infrastructure for addressing systemic regulatory and reimbursement issues in device development, as well as product-specific questions that arise within CIMIT investigators and its industrial collaborators.

Progress: During Year 2, Regulatory Affairs Initiative infrastructure was constant. The core team continues to identify and address regulatory and coverage/reimbursement issues both within CIMIT and across the medical device development community, as well as track important regulatory and coverage/reimbursement developments. Information is distributed throughout CIMIT via a monthly regulatory newsletter. Collaborations with Dr. Jonathan Rosen, Director of the Office of Technology Development, have identified a growing need to answer device-specific regulatory and coverage/reimbursement questions that arise during early stage product development with CIMIT.

Goal: Identify key regulatory and coverage/reimbursement issues facing the device development process across product lines ("systemic" issues).

Progress: Discussions with government and industry to identify and delineate issues continue. With regard to FDA-related matters, defining 'least burdensome means' under the Food and Drug Administration Modernization Act of 1997 (FDAMA) remains a concern and appears poised to move forward following the recent appointment of a new Director of the Office of Device Evaluation. FDA, industry, and healthcare institutions are assessing the potential impact of a new agency policy on the reuse of single-use medical devices, finalized in August 2000 and due for initial implementation in early to mid-2001. Finally, there is growing industry concern regarding the federal regulation of clinical trials for medical devices.

Focusing on coverage and reimbursement issues, both HCFA and industry appear anxious to make the medical device coverage and reimbursement process more transparent and reproducible. Legislation has been proposed to address perceived shortcomings in the present system and HCFA is reaching out to CIMIT for assistance in developing a more predictable internal process. In addition to these general issues, HCFA continues to widen its prospective payment systems and has initiated implementation of a hospital outpatient prospective payment system in August 2000.

Goal: Develop and apply a process for developing workable solutions to regulatory and reimbursement issues.

Progress: The Regulatory Affairs Initiative regulatory and coverage/reimbursement problem-solving process has developed three interrelated mechanisms to effect positive change in identified issues: 1) objective, scholarly white papers, 2) innovative solutions crafted in collaboration with stakeholders in the device regulatory and coverage/reimbursement process, and 3) CIMIT-sponsored forums directed at a specific issue(s).

During Year 2, three white papers addressing 'least burdensome means', HCFA coverage and reimbursement policies, and coverage/reimbursement for medically indicated procedures that use FDA-approved and non-approved devices, have been released for use in the CIMIT community.

Innovative solutions to systemic issues have taken a variety of forms. Following a successful demonstration, Dr. David Feigal, Director of the FDA's Center for Devices and Radiological Health, asked that CIMIT explore developing a web-based decision tree to assist both FDA reviewers and outside parties in implementing FDAMA's 'least burdensome means' requirement. The Coverage and Analysis Group at HCFA (CAG) has expressed interest in establishing a collaboration to make the coverage process more transparent and reproducible, a project that may incorporate the web-based technology developed for FDA as well as the technology assessment work of CIMIT's Dr. Scott Gazelle.

Planning for a CIMIT-FDA forum on 'least burdensome means' appears to be gaining momentum with the appointment of Dr. Bernard Statland as Director of FDA's Office of Device Evaluation. Currently, CIMIT-FDA discussions center on a videoconference to be held in collaboration with the agency and the Industry Least Burdensome Task Force.

Future Work: To release white papers on FDA's new policy regulating the re-use of single use medical devices and HCFA's hospital outpatient prospective payment system before year end. High-level discussions between the Director of Regulatory Affairs and FDA and HCFA in late September 2000, focused on strengthening and expanding current collaborations, and included the web-based 'least burdensome means' decision tree project.

5.3 Industrial Collaboration

It is essential that CIMIT's academic staff be able to collaborate effectively with those of industry, from early on in the life of a project. To achieve that, CIMIT's leadership has designed a unique three-level program for structured academic-industrial collaboration. This program, designed with the input of leaders from the relevant industries, is based on a foundation of a focussed industrial liaison program, with membership open to all sizes and types of companies. As a member of CIMIT's industrial liaison program, industry can gain access to an impressive interdisciplinary organization dedicated to developing minimally invasive technologies and expediting their transfer to the clinical setting. Industry can customize its participation to support research, consult with experts and gain valuable information from the clinical setting. CIMIT assigns an industrial liaison to assess the company's needs, define the ideal level of participation, and then manage the relationship to make sure that goals are met.

A second, more intense, level of interaction involves sponsored research to meet specific goals of mutual interest. CIMIT can provide the optimal environment within which to

work. CIMIT can coordinate key clinical and technology teams from multiple specialties to aid in corporate-sponsored research.

The most serious on-going level of mutual commitment, suitable for companies with major technological resources and presence in this market, is that of "strategic alliance partner". CIMIT's goal is to establish partnerships with a selected industry where each party contributes at their own expense whatever expertise, problem solving, research, development, prototyping, demonstration of feasibility and engineering is required with each party doing what it does best. Industry would be expected to provide the equipment and CIMIT would provide the technical and clinical evaluations as well as the assessment of the impact of the technology on clinical and financial outcomes.

We envision between four and ten major companies becoming members of the CIMIT Strategic Alliance. Because of the complexity in integrating the diagnostic and therapeutic equipment with the data/information systems, CIMIT can be a helpful vehicle to establish creative partnerships thought to be impossible in the past. No such partners have been selected as yet, but several are anticipated.

Underlying all of these interactions are a set of carefully crafted principles for the protection of intellectual property, and the fair and appropriate assignment of rights to inventions. Management attention is devoted to tracking intellectual property brought to the collaboration by partners, and that developed within the conduct of CIMIT projects.

The CIMIT consortium provides an unprecedented opportunity for successfully taking emerging minimally invasive technologies from bench to bedside. We are proud to offer industry a new model for product innovation -- where the developmental stage is compressed, where prospective technologies are assessed to measure their impact on healthcare outcomes, and where the rapid dissemination of effective new therapies into the clinical setting is encouraged. Beyond the specific set of relationships, we believe that CIMIT will make an important contribution to meeting the global challenge of achieving improved patient outcomes at reduced costs.

5.4 National CIMIT

CIMIT is working to expand its activities to the national (and international) scale. Several specific activities are national in scope; increased emphasis is also being given to broadening the national participation in our core activities.

Sponsored Student Research at Harvey Mudd College. For the third successive year, CIMIT is sponsoring an advanced undergraduate level project at Harvey Mudd College in Claremont, CA. This past year's activities involve the demonstration of a home health monitoring system..

Collaboration on Technology for Surgery Simulation. In both the CIMIT Simulation Program and the Operating Room of the Future/APRIL, collaborations are being built with leading centers (Stanford, Yale, Cleveland Clinic, etc.) to partition tasks (such development of high level software languages for anatomical modeling) and determine standards for equipment in the OR.

National Telestroke. CIMIT is leading the formation of collaborations to "roll-out" telestroke technology on a national scale. CIMIT initiated a collaborative research program in telemedicine "Remote Stroke Videoconferencing Project (RSVP): Telemedicine-Enabled Remote Diagnosis and Therapy" with Partners HealthCare System; and the plan is to migrate this program to a national scale,

Minimally Invasive Fetal Surgery Approved funding for a collaborative research program in minimally invasive fetal surgery "The Role of Mesenchymal Stem Cells in Fetal Tissue Engineering" at the Children's Hospital of Philadelphia,

Support of Combat Casualty Triage Device. Continued funding of the microwave research project "Application of Microwave Imaging to Rapid Non-Invasive Detection of Intracranial Hematoma" at USHUS.

Technology Assessment for Robotic Surgery. Held a joint meeting with Johns Hopkins University on technology assessment

5.5 Technology Development

Introduction

Beginning in February, 2000, CIMIT established a new Office of Technology Development (OTD) as a resource for its investigators and as a Core Program dedicated to the commercialization of innovative new medical technologies resulting from CIMIT supported activities.

During its first eight months of its operation, the OTD successfully focused on improving the documentation and initial processing of Intellectual Assets generated by CIMIT Investigators. This builds the foundation for ongoing activities, in which the OTD is expecting to execute several key CIMIT technology licenses and sponsored research agreements.

Primary Activities

- Encourage innovative scientists, engineers and clinicians to bring their collaborative proposals to CIMIT for funding consideration.

- Participate with the CIMIT Operations Committee to evaluate research proposals with particular emphasis on intellectual assets and corporate interactions.
- Facilitate institutional regulatory review and approval of CIMIT research involving pre-clinical and clinical testing programs.
- Assist in the early disclosure and processing of inventions related to the CIMIT projects to protect and expand the value of these patents.
- Provide preliminary patent searches to assist in defining claim structures and potential patentability assessments.
- Provide advocacy for CIMIT investigators in preliminary and advanced discussions with potential corporate partners.
- Assist the licensing offices of the CIMIT Consortium institutions in designing consulting, non-disclosure, sponsored research, clinical research, licensing and related agreements.
- Conduct studies on relevant health care trends, technology developments, market and reimbursement opportunities and international biomedical research directions to assist Investigators and licensing offices in correctly valuing CIMIT supported technology innovations.
- Assist CIMIT investigators in the design of their longer-range research plans.
- Provide educational opportunities to instruct CIMIT investigators in intellectual asset management, regulatory strategies and project planning and management techniques.

The CIMIT Office of Technology Development works closely with the CIMIT Operations Committee, the other CIMIT Core Programs, the Licensing Offices and the private investment community to help assure the smooth, efficient and productive evolution and eventual transfer of CIMIT supported technologies.

The "Enterprise Fund"

The Office of Technology Development has worked closely with the MGH and Partners Development Offices to establish a dedicated CIMIT Resource, funded by private philanthropic gifts, to assist later-stage CIMIT technology development efforts. These funds will be used to bring investment opportunities to the attention of the private investment community and to facilitate the formation of new ventures founded on the successful transfer of CIMIT supported technologies. CIMIT and the Consortium Institutions are currently exploring the legal, tax, and related issues associated with equity participation in these ventures.

Summary

In the future, the OTD is planning to activate a dedicated resource designed to prepare suitable CIMIT technologies for private venturing opportunities.

In each of its activities, the CIMIT Office of Technology Development seeks to improve the efficiency of the CIMIT funding process, facilitate the productivity of the CIMIT investigators, and explore innovative exit strategies designed to maximize the ultimate health care impact of CIMIT supported technologies.

6.0 CIMIT Operations

6.1 Management of Resources

Background:
CIMIT (as The Center for Minimally Invasive Therapy) was created in 1993 by MGH physicians with the conviction that high technology could be better utilized to improve patient care. The initial work was supported by the hospital; it was predominately clinical in focus, with limited central or core activities. To solidify working relationships, provide a central leadership capability and establish a wider research base, the CIMIT Consortium was formed, and DoD support was solicited in 1998. Research was divided into two broad categories: Clinical Focus Areas ("tech pull") and Advanced Technology Teams ("tech push"), and mechanisms such as the CIMIT Forum were set up to stimulate collaboration. The importance of the military healthcare mission was recognized, and collaborations with military staff were initiated. The well-established process of physician leadership for the major programs was maintained.

Research in the first two years (FY99-00) was directed toward the major clinical challenges: Cardiovascular Disease, Cancer, Stroke, and Trauma, and a variety of attractive technologies. It became clear that strong, committed clinical champions were needed to lead these programs, due to the required project scale and the broad professional attitude required to accept and adopt new approaches. Three of the current Program Leaders (Dr. Muller in Vulnerable Plaque, Dr. Vacanti in Tissue Engineering, and Dr. Oesterle in Endovascular Devices) were recruited to the MGH and to CIMIT to establish those programs.

Also in that period, the Education and the Outcomes Assessment programs were begun to assist investigators, and the Industrial Liaison activities established to provide linkages for commercialization and shared development.

By the end of the first year, the opportunities for the unique role and contribution to be made by CIMIT were clear. Two major activities were initiated: (1) To refocus and recommit the CIMIT community (accomplished though a series of working sessions in the latter half of FY 00), and (2) To establish an Operations Committee formed of experienced leaders in successful medical technology development.

Mission Statement:
The prior mission statement was too narrow in focus to highlight the innovative structure and function of CIMIT, both in terms of interdisciplinary teams, as well as the focus of innovative technology, which emphasizes but is not exclusively focused on minimally invasive diagnosis and therapy. The mission statement now reads:
"To improve patient care by bringing together scientists, engineers, and clinicians to catalyze development of innovative technology, emphasizing minimally invasive diagnosis and therapy."

While CIMIT's range of application has broadened (as reflected in the change of name to Center for the Integration of Medicine and Innovative Technology), the approach has sharpened, to best leverage the extensive research at the participating partners. Criteria for supporting Projects (formerly "Tasks") became:

- The work meets peer review metrics for uniqueness, quality, and contribution.
- The Project is multi-disciplinary, and preferably multi-institutional, outside of the normal academic patterns of collaboration.
- There is an apparent, if not immediate, path to clinical or CCC impact, including the steps beyond the period of CIMIT support.
- If successful, the work will advance the field significantly toward the long-term goals.
- CIMIT's non-financial resources (synergy, core programs, leadership, mentoring) will add value.

As well, the Year 2 Retreat resulted in a re-structuring of the science awards process and a redesign of the major programs. Through the application of the new awards criteria (listed above) the existing CFA and ATT tasks were reformed into eight Programs: Simulation, Minimally Invasive Surgery, Image-Guided Therapy, Tissue Engineering/ Biomaterials, Endovascular Devices, Trauma/Critical Care, Stroke, and Vulnerable Plaque. Other new efforts include developing five year plans from the directors of the major programs, and a structured process for establishing multiyear funding, with periodic review and continuation based on scientific and technical goals achieved, dependent of course on availability of funds.

The granting process for science awards was revised, with a focus on stimulating junior scientists to apply, as well as supporting respected senior scientists who can further the work of CIMIT. The science grants include: New Concepts (up to $25,000); Proof-of-Principal (up to $75,000) and Application Development (up to $250,000). The major determinants of funding will be aspects of project quality (clinical need, scientific merit, and innovation) and project design (fit within CIMIT focus, degree of collaboration, clarity of milestones, and defined exit strategy). In addition to these three, there are major program awards, which provide more substantial and longer term support that fosters CIMIT's presence in areas of strategic importance. This proposal outlines eight major areas of focus, under which many science award applications will fall; as well as new initiatives.

Other awards available through CIMIT are Fast Forwards, which are designed to allow fast tracking of a new technology or technique to be brought into the Partners System; as well as Individual Career Development Awards, including student, fellow, faculty, and senior investigator awards.

Management Structure and Roles

During Year 2, CIMIT's management structure was split into two levels: The Office of the Director and the Operations Committee. The Operations Committee oversees the day-to-day activities of CIMIT and ensures continued progress and focus of the programs. The Operations Committee is comprised of experienced leaders ("Associate

Directors") who devote over 70% of their professional time to the furthering of the science, management, and integration functions of the major programs and activities of CIMIT. The Operations Committee evaluates submitted programs for Scientific Merit, (utilizing external peer review, as appropriate) and fit to the Project criteria listed above.

The Operations Committee and Program Leaders are senior basic and clinical researchers with strong histories of prior funding, publication and clinical expertise. The investigator population is a mix of respected senior and promising junior scientists drawn from the Consortium institutions and the Department of Defense.

Each Associate Director who is a member of the Operations Committee has responsibility and oversight for each award granted through CIMIT, as well as the general focus and progress of each major program area.

6.2 Impact of CIMIT on the technical direction and organization of the ongoing Programs

Simulation
During 2000, the Simulation Program integrated two previously separate research groups through funding of joint scientific projects. The Center for Medical Simulation and the CIMIT Simulation Group are collaborating to develop the Trauma Surgery Decision System. These two groups, which had separate facilities, will now work together in the new CIMIT headquarters on Landsdowne Street adjacent to the MIT campus. Within the Landsdowne building, the simulation program will work in close proximity to the Operating Room of the Future/APRIL Project. As new procedures are developed in this experimental facility, the simulation teams will insert new training methods and model new devices and procedures. As the Endovascular Devices and Stroke Programs develop new devices and procedures, the Simulation Group will participate in parallel to create modeling and deployment scenarios as needed, before devices are introduced to the general medical profession.

Minimally Invasive Surgery
CIMIT, fulfilling its central purpose, has created this program by melding engineers, scientists, and clinicians to work together to resolve the complex issues of the Advanced Procedure Room. CIMIT is constructing a laboratory environment for these teams to use together in a 15,000 square foot facility immediately adjacent to the MIT campus. This facility will also house the Simulation Program (described above) and so will further enhance the ability to simulate and test the new procedures. Also, CIMIT has created a novel flexible, integrated operating room devoted to minimally invasive surgery at the Massachusetts General Hospital. This facility will provide the environment in which the clinical utility of new concepts and procedures can be evaluated and outcomes assessed, and in which the impact of the new devices and technologies on staffing requirements and productivity can be tested.

Image Guided Therapy

The primary contribution of CIMIT to Image Guided Therapy Programs has been to enable proof-of-principle experiments. One completed project has transitioned beyond CIMIT funding: the lung volume reduction technology has formed the basis for a spin-off company. Technology capabilities developed in this program have been also been transferred to other CIMIT programs. In particular, the techniques developed by the Surgical Planning Laboratory have been used in the program for distraction osteogenesis. and are planned for use in the acute stroke laboratory .

Tissue Engineering and Biomaterials

Through CIMIT, the MGH team was introduced to the advanced MEMS technology available at the Draper Lab, and this collaboration, combined with the biomaterials research program, form the technological core of the Tissue Engineering Program. CIMIT has enabled these projects to go forward in the following ways:

1. The creation of an extensive network of collaboration in areas of technological expertise, biologic expertise, and clinical expertise:

MGH – Department of Surgery	MGH – Other Departments
Pediatric – Tumor Control	Cardiology – Heart Muscle, Blood Vessels
Cardiac – Heart Valves	Pathology – Liver Development
Maxillofacial – Mandible	Cutaneous Biology Research Center-
Urology – Nerves at Prostate	Skin and Tumor Control
Vascular – Blood Vessels	
Thoracic – Esophagus	
Gynecology – Ovary and Tubes	

   Other Institutions: Harvard Center for Genomic Research (Liver), Forsyth Dental Institute and Harvard School of Dental Medicine (Teeth), Brigham and Women's Hospital and University of Michigan (Intestine), University of Massachusetts (Spinal Cord), Shriner's Burn Institute (Skin), Children's Hospital (Heart Valves)
2. The funding of core programs in vital organs and vascularized tissue leading to a new approach in Tissue Engineering – significant new intellectual property allowing for the next step of industrial support and commercial development.
3. Seed money for individual projects to bring them to clinical trials:
   - Human cartilage for ear
   - Bone for mandibular or craniofacial repair
   - Peripheral nerve
   - Blood vessel replacement

Endovascular Tools

This project would not have been initiated without CIMIT support, which provided essential funding for the recruitment and research of key investigators. Through CIMIT, the intravascular device laboratory has been fully integrated with the CIMIT Tissue Engineering Projects. We plan on forging a deep collaboration with the NMR Center at the MGH to investigate quantitative imaging of our cellular transplants. The Office for Licensing at CIMIT has been effectively involved in securing the necessary Materials Transfer Agreements to allow this project to move to the next stage.

The Cell Transfer program is broadly integrated with three of the four consortium partners of CIMIT. Within CIMIT, we are actively collaborating with the Tissue Engineering Program. Through this Program, we have extensive contact with related laboratories at MIT, which will continue to collaborate on the development of BioGels as a vehicle for cell transplantation. The gene transfer elements of this program have been integrated with the laboratories of the MGH Cardiovascular Research Group. CIMIT has provided an environment, free of departmental boundaries, where we can pursue this expansive initiative with enthusiasm and unquestioned support.

Trauma and Critical Care

CIMIT has been instrumental in the RAFT project's rapid progress from *in vitro* testing through *in vivo* validation, as RAFTS now prepares to enter clinical trial. The CIMIT funding level has ensured sufficient personnel and appropriate equipment to make this expeditious advance from bench to bedside (in 2 years). Since the beginning, there has been a close collaboration between the military and civilian groups. The core project team consists primarily of active duty military physician-scientists who represent the 3 medical corps branches, i.e., army, navy and air force. This group is composed of soldiers, sailors and airmen assigned to USUHS, WRAMC and NNMC (National Naval Medical Center). The core team collectively works closely with Dr. Riechers and his civilian engineering firm, Spectra Research in Ohio. Statistical and data processing (including software modification) work includes the efforts of Dr. Lockhart and his civilian firm, MedSciStat in California. The development of RAFTS as a diagnostic tool for point of care application, especially pre-hospital, is part of an overall effort to develop technology for trauma, critical care and emergency medicine. This effort is lead by Dr. Puyana of the Brigham and Women's Hospital.

In addition to CIMIT's financial support of the MicroCanary Sensor, the CIMIT staff has been instrumental in connecting the technologists at Draper with the physicians at Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) to arrive at an appropriate and valuable integration of technology and medicine. This integration is necessary for identifying relevant applications of the technology as well as providing a complementary medical knowledge and experience base. Collaboration between the Draper and BWH or MGH champions has been fundamental to identification and development of the MicroCANARY sensor platform for both cytokine detection and microbial detection.

Stroke

The stroke program is a collaborative effort between investigators from Neurology, Neurosurgery, the NMR Center, and the CIMIT-sponsored DATA group. The collaborative scaffold of CIMIT has led to an interdisciplinary project that should have major effect on triaging new stroke technology into the medical system. CIMIT is the only platform in the institution that provides a home for multidisciplinary teams to attack a serious medical problem. The CIMIT stroke CFA is a clear testament to CIMIT's ability to catalyze projects that could never have been envisioned or carried out within the walls of a single academic department. In addition, there are interactions with other CIMIT activities including Vulnerable Plaque and Image Guided Therapy.

Vulnerable Plaque

In addition to interactions within the vulnerable plaque activites, investigators are provided with opportunities to collaborate with other CIMIT DoD funded investigators. There are ongoing interactions with members of the CIMIT Stroke CFA exploring a variety of imaging techniques for the assessment of carotid disease and in the detection and treatment monitoring of stroke patients. The ability of noninvasive imaging techniques to provide a "roadmap" of coronary plaque distribution and intravascular imaging to target specific lesions will enable direct collaboration with the CIMIT Device program. Imaging data will enhance the guidance of conventional intravascular therapy and influence the development of novel devices for the local treatment including novel catheter and other device-pharmaceutical combinations.

7.0 Summary

The use of technology has revolutionized health care; and the capabilities now being developed have the potential to make even more dramatic changes. While the explosive growth in areas such as imaging, robotics, fiber optics, high-speed computing and biomedical engineering have demonstrated vast potential for medical use, the challenge of successfully taking these technologies from bench to bedside remains.

CIMIT was started in 1994 to address this challenge, with seed funding from philanthropy and the Massachusetts General Hospital. CIMIT received major federal funding through the Department of Defense beginning in 1998. The CIMIT Programs have been:

Clinical Focus Areas: (CFAs)	Cardiovascular Disease	Cancer	Stroke
	Trauma and Critical Care	New Initiatives	

Advanced Technology Teams (ATTs)

Technology Assessment and Outcomes Analysis

A major goal of CIMIT is to provide new medical technology of value to the Department of Defense. Special emphasis is given to development of technology to improve the care of combat casualties.

Through DoD's support, CIMIT has assembled a superb team of clinicians, scientists and researchers to lead its scientific programs and a management team with experience and expertise in operations, technology development, and program management. CIMIT also supplies mechanisms to facilitate technology transfer and ultimate application to patient care. Programs in Technology Development, Industry Collaboration, Regulatory Affairs, and Education have been developed to facilitate its work.

CIMIT catalyzes collaborations that are monitored, measured, and analyzed for their ultimate application in acute care in the field, as well as in the clinical setting. These innovative projects would not have occurred in a traditional environment. CIMIT has delivered significant results in all its programs, some of the major accomplishments this past year are listed below.

Major Accomplishments

Clinical Focus Areas:

- Demonstrated efficacy of novel tissue sealant applied to the anastomosis of minimally invasive coronary bypass procedure in a large animal model;
- Demonstrated utility of Zeus Robotic Surgical System and Heartport cardiopulmonary bypass techniques in large animal model;
- Developed a small animal model for activation of endothelial cells in the lining of the cardiovascular system:

- Demonstrated optical techniques to detect early hemorrhage and continuously monitor brain hemodynamics;
- Developed innovative techniques to diagnosis and treat acute stroke;
- Developed animal model for proton beam treatment of intractable epilepsy;
- Demonstrated image-guided focused ultrasound to treat cancer;
- Development and application of novel Optical Coherence Tomography (OCT) techniques to detect vulnerable plaque in blood vessels and abnormal tissue in the GI tract;
- Optical techniques to determine tissue and organ status (pH, pO2, pCO2) in trauma and critical care settings;
- Developed lung volume reduction techniques for treatment of emphysema; and
- Developed computer-based, three-dimensional image treatment planning system for endoscopically placed distraction device.

Advanced Technology Teams:

- Development of a polymer-based gene delivery platform;
- Design, fabrication and testing of a 3-dimensional culture system for tissue engineering;
- Developed image-guided, segmentation techniques based on adaptive filtering;
- The simulator system developed jointly by CIMIT and Mitsubishi for fluoroscopic catheterizations is now being used commercially by Guidant for customer training.
- Development of a micro-electro-mechanical silicon (MEMS) platform for bioassay;
- MEMS may be used for:
    - predicting multiple organ failure (MOF);
    - measuring blood components;
    - pathogen detection;
    - development of novel approaches for tissue engineering.
- Development of animal models for minimally invasive meniscal repair;

Technology Analysis and Outcomes Assessment:

- Stroke CFA: Established database with over 7,000 patients treated for cerebrovascular disease. This data base can be used for cost/benefit analysis of stroke treatment.
- Image Guided Therapy Program: Completed a cost-effectiveness analysis for surgical resection of liver metastases, Analyzed the benefit of Optical Coherence Tomography in upper gastrointestinal disorders.

Organizational Evolution

By the end of the first year, the opportunities for the unique role and contribution to be made by CIMIT were clear. Two major activities were initiated: (1) To refocus and recommit the CIMIT community (accomplished though a series of working sessions in the latter half of FY 00), and (2) To establish an Operations Committee formed of experienced leaders in successful medical technology development. The mission statement now reads:

"To improve patient care by bringing together scientists, engineers, and clinicians to catalyze development of innovative technology, emphasizing minimally invasive diagnosis and therapy."

Conclusions

CIMIT has thus evolved and grown, while preserving its core commitment to promote the adoption of technologies to address unmet healthcare needs. The ongoing programs are strong, and all have recorded significant accomplishments in the past year. There are several examples of project evolution beyond CIMIT, into commercialization or larger scale sponsored research. CIMIT has mechanisms for self-renewal and capacity for growth, which will ensure its long term success.

8.0 REFERENCES/Bibliography

CIMIT Publications: Original Reports

Ay H, Ay I, **Koroshetz WJ**, Finklestein SP. Potential usefulness of basic fibroblast growth factor as a treatment for stroke. Cerebrovasc. Dis. 9:131-135, 1999.

Ay H, Buonanno FS, Abraham SA, Kistler JP, **Koroshetz WJ**. Electrocardiographic diagnosis of patent foramen ovale associated with ischemic stroke. Stroke 29:1393-1397, 1998.

Ay H, Buonanno FS, Schaefer PW, Le DA, Wang B, **Gonzalez RG**, Koroshetz WJ. Posterior leukoencephalopathy without severe hypertension. Utility of diffusion-weighted MRI. Neurology 51:1369-1376, 1998.

Ay H, Furie KL, Yamada K, **Koroshetz WJ**. Diffusion-weighted MRI characterizes the ischemic lesion in transient global amnesia. Neurology 51:901-903, 1998.

Ay H, Oliveira-Filho J, Buonanno FS, Ezzedine M, Schaefer PW, Rordorf G, Schwamm LH, **Gonzalez RG**, Koroshetz WJ. An Identifiable Subset of Lacunar Infarctions Caused by Embolism. Stroke 30(12):2644-2650, 1999.

Ay H, **Gonzalez RG**, Buonanno FS, Rordorf G, Schaefer PW, Schwamm LH, Yamada K, Sorensen GA, Koroshetz WJ. Normal Diffusion-Weighted MR Imaging During Stroke-Like Deficits. Neurology 52: 1784-1792, 1999.

Bauer JJ, Magee JH, Moses G, Leitch R, **Dawson SL**. Medical simulation training initiative (MSTI), SPIE Conference on Battlefield Biomedical Technologies 4037:254-263, 2000.

Ben-Ur E. Development of a force feedback laparoscopic surgery simulator. Master's Thesis. Massachusetts Institute of Technology, September 1999.

Ben-Ur E, **Salisbury K**. A 5 F haptics device for laparoscopic surgery simulation. SPIE Conference on Battlefield Biomedical Technologies. Proc SPIE (in press) 2000.

Bizheva KK, Siege AM, **Boas DA**. Pathlength resolved dynamic light scattering in highly scattering random media. Phys Rev E 58:7664-766, 1998.

Blank SD, Lahorra JA, McDonald RS, Denenberg AG, Titus JS, **Torchiana DF**, Dagget WM, Geffin GA. Superior recovery of hypertrophied rat myocardium after cardioplegic arrest. Ann Thorac Surg 65(2):390-396, 1998.

Boas DA, Bizheva KK, Siegel AM. Using dynamic low coherence domain interferometry to image brownian motion within highly scattering media. Opt Lett 23:319-321, 1998.

Boppart SA, Deutsch TF, **Rattner DW**. Optical Imaging Technology in Minimally Invasive Surgery. Surg Endosc 13:718-722, 1998.

Bouma BE, Tearney GJ, Compton CC, Nishioka NS. High resolution imaging of the upper gastrointestinal tract *in vivo* using optical coherence tomography. Gastro Endosc (in press) 2000.

Bouma BE, Tearney GJ. Power-efficient nonreciprocal interferometer and linear-scanning fiber-optic catheter for optical coherence tomography. Optical Soc Amer 24(8):531-533, 1999.

Cheng X, **Boas DA**. Diffuse optical reflection tomography with continuous illumination. Optics Express 3:118-123, 1998.

Cheng X, **Boas DA**. Systematic diffuse optical image errors resulting from uncertainty in the background optical properties. Optics Express 4:299-307, 1999.

Chung AH, **Jolesz FA**, Hynynen K. Thermal dosimetry of a focused ultrasound beam *in vivo* by magnetic resonance imaging. Med Phys 26(9): 2017-2026, 1999.

Cingo NA, Soller BR, **Puyana JC**. Multivariate calibration modeling of liver oxygen saturation using near-infrared spectroscopy. Proc SPIE 3911:230-236, 2000.

Cotin SC, **Dawson SL**. CAML: a general framework for the development of medical simulation systems. SPIE Conference on Battlefield Biomedical Technologies (in press) 2000.

Cramer S, **Koroshetz WJ**, Schwamm L, Buonanno F, Rordorf G. Predictors of mortality in stroke patients admitted to an intensive care unit. Critical Care Medicine (in press) 2000.

Cunningham BT, Regan R, Weinberg M, Clapp C, Hildebrant E, Williams J. Miniature silicon biological assay chip and applications for rapid battlefield diagnostics. Proc Aerospace Sympos (in press) 2000.

Dawson SL, Cotin S, Meglan D, Shaffer DW, Ferrell MA. Simulation for Interventional cardiology training. Submitted for publication, 2000.

Dawson SL, Cotin S, Meglan D, Shaffer DW, Ferrell MA. Designing a computer-based simulator for interventional cardiology training. Catheterization and Cardiovascular Interventions (in press) 2000.

Dawson SL, Kaufman JA. The imperative for medical simulation. Proc IEEE 86(3):479-483, 1998.

Gollard P, Kikinis R, Halle M, Umans C, **Grimson WEL**, Shenton ME, Richolt JA. A novel approach to visualization and integration of medical information. AnatomyBrowser 4:129-143, 1999.

Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, Wang B, Sorensen AG, Koroshetz WJ. Diffusion-weighted MR imaging: Diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology 210:155-162, 1999.

Grimson EWL, Kikinis R, Jolesz FA, Black PM. Image-guided surgery. Sci Amer 280(6):62-69, 1999.

Hynynen K., McDannold N., Mulkern RV, **Jolesz FA**. Temperature monitoring in fat with MRI. Magn Reson Med 43:901-904, 2000.

Kaczka DW, **Ingenito EP**, Israel E, Lutcheon KR. Airway and lung tissue mechanics in asthma: effects of albuterol. Am J Respire Crit Care Med 159:169-78, 1999.

Kaihara S, Borenstein J, Koka R, Lalan S, Ochoa ER, Ravens M, Pien H, Cunningham B, Vacanti JP. Silicon micromachining to tissue engineer branched vascular channels for liver fabrication. Tissue Engineering 6(2):105-117, 2000.

Kaihara S, **Vacanti JP**. Tissue engineering: toward new solutions for transplantation and reconstruction surgery. Arch Surg 134(11):1184-1188, 1999.

Kettenback J, Wong T, Kacher D, Hata N, Schwartz RB, Black PM, Kikinis R, **Jolesz FA**. Computer-based imaging and interventional MRI: applications for neurosurgery. Comput Med Imaging Graph 23(5):245-258, 1999.

Kolh PH, **Torchiana DF**, Buckley MJ. Atheroembolization in cardiac surgey: the need for preoperative diagnosis. J Cardiovasc Surg 40:77-81, 1999.

Langer RS, **Vacanti JP**. Tissue Engineering: the challenges ahead. Scientific American April:86-89, 1999.

Lev MH, Farkas JJ, Gemette J, , Schwamm LS, **Koroshetz WJ**, Gonzalez RG. Advantage of soft CT windowing and level vs. hard copy evaluation of CT scan in hyperacute stroke. Radiology 213(1):150-155, 1999.

Leykin L, Libenzon L. Lasers in assisted reproductive technology. Assisted Production 9(2):112-116, 1999.

Ling GSF, Riechers RG, Pasala KM. Diagnosis of subdural and intraparenchymal intracranial hemorrhage using a microwave based detector. Proc Int'l Soc Optical Engineering 4037:212-217, 2000.

Ling GSF, Riechers R, Pasala KM, Riechers R, Zeidman SM. *In vivo* validation of microwave detection of intracranial hemorrhage. Proc. Int'l Soc. Optical Engineering 3712:18-25, 1999.

Ling GSF, Day KD, Rhee P, and Ecklund JM. In search of technological solutions to battle field management of combat casualties. Proc. Int'l Soc. Optical Engineering 3712:1-8, 1999.

Lynn DM, **Langer RJ**. Degradable Poly(β-Amino Esters): synthesis, characterization, and self-assembly with plasmid DNA. Amer Chem Soc (in press) 2000.

Manno EM, **Koroshetz WJ**. Cerebral blood flow. Neurosonology (in press) 2000.

McDannold N, Hynynen K, **Jolesz FA**. MRI monitoring of the thermal ablation of tissue with a long exposure time. Submitted for publication, 2000.

McDannold NJ, Hynynen K, Oshio K, Mulker RV, **Jolesz FA**. Temperature monitoring with line scan echo planar spectroscopic imaging (LSEPSI). Med Phys Submitted for publication, 2000.

McDannold NJ, King RL, **Jolesz FA**, Hynynen KH. Usefulness of MR imaging-derived thermometry and dosimetry in determining the threshold for tissue damage induced by thermal surgery in rabbits. Radiology 216(2):517-523, 2000.

Mycek MA, Schomacker KT, **Nishioka NS**. Colonic polyp differentiation using time-resolved autofluorescence spectroscopy. Gastrointest Endosc 48(4):390-394, 1998.

Niklason LE, Gao J, Abbott WM, Hirschi KK, Houser S, Marini R, **Langer R**. Functional arteries grown *in vitro*. Science 284:489-493, 1999.

Nishioka NS, Schomacker KT. Mucosal exposure to light during routine endoscopy. Gastrointestinal Endosc 49(4):456-461, 1999.

Nishioka NS, Mycek MA. Initial experience with real-time video processor for enhancing endoscopic image contrast. Gastrointest Endosc 48(1):62-66, 1998.

Ottensmeyer M, **Salisbury K**. TEMPEST, a tissue measurement tool. SPIE Conference on Battlefield Biomedical Technologies (in press) 2000.

Ottensmeyer M, **Salisbury K**. *In vivo* mechanical tissue property measurement for improved simulations. Submitted for publication.

Padwa BL, Kearns GJ, Todd RC, Troulis MJ, Mulliken, JB, **Kaban LB**. Simultaneous Maxillary and Mandibular Distraction Osteogenesis with a Semiburied Device. Int J Oral & Maxillofac Surg 28:2-8, 1998.

Paithankar DY, Schomacker KT, **Nishioka NS**. Frequency-domain optical detection of subsurface blood vessels: Experimental and computational studies using a scattering phantom. IEEE J Selected Topics in Quant Electron 5:1032-1039, 1999.

Provenzale JM, **Sorensen AG**. Diffusion-weighted MR imaging in acute stroke: theoretic considerations and applications. Am J Roentgenol 173(6):1459-1467, 1999.

Puyana JC, Soller B, Zhang S, Heard S. Continuous Measurement of Gut pH with Near-infrared Spectroscopy during Hemorrhagic Shock. J of Trauma 46:9-15, 1999.

Puyana JC, Soller B, Zhang S, Micheels R, Heard S. Noninvasive near infrared spectroscopic assessment of abdominal wall muscle pH in hemorrhagic shock and its relationship to gastric intramucosal pH. Surgical Forum Vol. XLIX, 1998.

Rattner DW. Beyond the Laparoscope: minimally invasive surgery in the new millennium. Surgery 125:19-22, 1999.

Rattner DW. Future directions in innovative minimally invasive surgery. Lancet 353(suppl 1):12-15, 1999.

Riechers R, Pasala KM, **Ling GSF**. Microwave detection system for locating hemorrhage sites within the cranium and other regions. Proc Int'l Soc Opt Eng 3253:165-176, 1998.

Rordorf G, **Koroshetz WJ**, Copen WA, Cramer SC, Schaefer PW, Budzik RF, Schwamm LH, Buonanno F, Sorensen AG, Gonzalez RG. Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI. Stroke 29:939-943, 1998.

Rordorf G, **Koroshetz WJ**, Copen WA, Gonzalez G, Yamada K, Schaefer PW, Schwamm LH, Ogilvy CS, Sorensen AG. Diffusion- and perfusion-weighted imaging in vasospasm after subarachnoid hemorrhage. Stroke 30:599-605, 1999.

Santini JT Jr, Cima MJ, **Langer R**. A controlled release microchip. Nature 397:335-338, 1999.

Saver JL, Johnston KC, Homer D, Wityk R, **Koroshetz WJ**, Truskowski LL, Haley EC. Infarct volume as a surrogate or auxiliary outcome measure in ischemic stroke clinical trials. Stroke 30:293-298, 1999.

Saxena AK, Marler J, Benvenuto M, Willital GH, **Vacanti JP**. Skeletal muscle tissue engineering using isolated myoblasts on synthetic biodegradable polymers: preliminary studies. Tissue Eng 5(6):525-532, 1999.

Schwamm L, **Koroshetz WJ**, Sorensen AG, Wang B, Copen WA, BudzikR, Rordorf G, Buonanno FS, Schaefer PW, Gonzalez G. Time course of lesion development in patients with acute stroke: Serial diffusion and hemodynamic -weighted magnetic resonance imaging. Stroke 29:2268-2276, 1998.

Seldin EB, Troulis MJ, **Kaban LB**. Evaluation of a Semiburied Fixed-Trajectory Curvilinear Distraction Device in an Animal Model. J Oral & Maxillofac Surg 57(12):1442-1448, 1999.

Shaffer DW, **Dawson SL**, Muller J. Current Perspective: Design principles for the use of simulation as an aid in interventional cardiology training. Submitted for publication, 2000.

Shaffer D, Meglan D, Ferrel M, Dawson SL. Virtual rounds: simulation-based education in procedural medicine. In: Pien H, editor. Battlefield Biomedical Technologies, Proc SPIE 3712:99-108, 1999.

Shum-Tim D, Stock U, Hrkach J, Shinoka T, Lien J, Moses MA, Stamp A, Taylor G, Moran AM, Landis W, Langer R, **Vacanti JP**, Mayer JE, Jr. Tissue engineering of autologous aorta using a new biodegradable polymer. Ann Thorac Surg 68(6):2298-2304, 1999.

Siegel AM, Marota JA, **Boas DA**. Design and evaluation of a continuous-wave diffuse optical tomography system. Optics Express 4:287-298, 1999.

Sodian R, Hoerstrup SP, Sperling JS, Daebritz S, Martin DP, Schoen FJ, **Vacanti JP**, Mayer JE. Tissue engineering of heart valves: *in vitro* formation of viable tissue. J Heart Valve Disease (in press) 2000.

Soller BR, Cingo N, **Puyana JC**, Khan T, Hsi C, Kim H, Favreau J, Heard SO. Simultaneous measurement of hepatic tissue pH, venous oxygen saturation and hemoglobin by near infrared spectroscopy. Shock (in press) 2000.

Soller BR, Cingo N, **Puyana JC**, Khan T, Hsi C, Favreau, J, Heard SO. Regional hepatic dysoxia during hemorrhagic shock in swine. Submitted for publication, 2000.

Sorensen AG, Copen WA, Østergaard L, Buonanno FS, Gonzalez RB, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, **Koroshetz WJ**. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology 210:519-527, 1999.

Sorensen AG, Wu O, Copen WA, Davis TL, **Gonzalez RG**, Koroshetz WJ, Reese TG, Rosen BR, Wedeen VJ, Weisskoff RM. Detection of changes in water diffusion anisotropy in human acute cerebral ischemia using MRI. Radiology 212(3):785-792, 1999.

Sorensen AG, Wu O, Hakan A, **Koroshetz WJ**, Finklestein S. Functional MRI determinants of tissue at risk in acute human stroke: effect of basic fibroblastic growth factor. Stroke (in press) 2000.

Sorensen AG, Wu O, Yamada K, Vaughan JT. Clinical MRI at 3.0 Tesla: Preliminary *ex vivo* animal and *in vivo* human safety studies. Stroke (in press) 2000.

Sundback CA, **Vacanti JP**. Alternatives to liver transplantation: from hepatocyte transplantation to engineered organs. Gastroent 118(2):438-442, 2000.

Troulis MJ, Perrott D, **Kaban LB**. Endoscopic mandibular osteotomy, replacement and activation of a semi-buried distractor. J Oral & Maxillofac Surg 57(9):1110-1113, 1999.

Troulis MJ, Padw, B, **Kaban, LB**. Distraction osteogenesis: past, present, and future. Facial Plast Surg 14(3):205-215, 1998.

Troulis MJ, Glowacki J, Perrott, DH, **Kaban LB**. Effects of latency and rate one bone formation in a porcine mandibular distraction model. J Oral & Maxillofac Surg (in press) 2000.

Vacanti JP, Langer RS. Tissue engineering: the design and fabrication of living replacement devices for surgical reconstruction and transplantation. The Lancet 354 (suppl I):32-34, 1999.

Westin CF, Richolt J, Moharir V, Kikinis R. Affine adaptive filtering of CT data. Medical Image Analysis 4(2):1-19, 2000.

Zientara GP, Saiviroonporn P, Morrison P, Fried MP, Hushek SG, Kikinis R, **Jolesz FA**. MRI monitoring of laser ablation using optical flow. J MRI 8:1306-1318, 1998.

CIMIT Publications: Abstracts and Presentations

Bizheva K, **Boas DA**. Wave model of the effect of multiply scattered light in confocal and optical coherence microscopes. SPIE/BioS West, Jan. 1999, San Jose, CA.

Boas DA, Cheng X. Near infrared spectroscopy of focal hemoglobin Changes. International Symposia on Industrial Lasers and Biomedical Optics IL'99 and BiOS'99, October 1999, Wuhan, China.

Boas DA, Bizheva K. The effects of multiple light scattering on optical coherence tomography. Summer School on Waves and Imaging through Complex Media, Aug. 30 - Sept. 3, 1999, Cargese, Corsica, France.

Boas DA, Siegel AM, Cheng X, Chance B. An effective continuous-wave diffuse optical tomography system for anatomical and functional tissue imaging. SPIE Photonics China, Sept.16-19, 1998, Beijing, China.

Boas DA. Diffuse optical tomography: The basics," Human Brain Mapping, June 1999, Dusseldorf, Germany.

Boas DA. Imaging in the single scattering, few scattering, and light diffusion regimes with low-coherent light. SPIE/BioS West, Jan. 1999, San Jose, CA.

Boas DA. Optical imaging in tissue (Mammography). OSA Annual Meeting, Workshop on Emerging Technologies in Biomedical Optics, Oct. 7, 1998, Baltimore, MD.

Boas DA. Optical Imaging: Seeing into the future. Harvard Medical School Department of Continuing Education course on Clinical Functional MRI, Oct. 13-15, 1998, Boston, MA.

Boas DA. Optical Mammography. Engineering Foundation Conference, Aug. 1-5, 1999, Kona, Hawaii.

Boas, DA, Gaudette TJ, Wang, L, Ay, H, Koroshetz, W, Sorensen, G. Preliminary investigation into the use of diffuse optical tomography for monitoring and imaging Stroke 3712-07.

Bogdanov A Jr., Matuszewski L, Bremer C, **Gimbrone M Jr.**, Weissleder, R. Enzyme-mediated polymerization of paramagnetic contrast agent for MR signal amplification in molecular imaging. Submitted to The Radiological Society of North America Meeting, Chicago, IL 12/2000.

Bouma BE. Endoscopic optical coherence tomography of the gastrointestinal tract. Gastrointestinal Endoscopy. Vol. 49, No. 4, part 2, AB152:390. ASGE Meeting, DDW, May 15-19, 1999, Orlando Fl.

Brand S, Wang TD, Schomacker KT, Compton CC, **Nishioka NS**. Diagnosis of high-grade dysplasia in Barrett's esophagus using 5-aminolevulinic acid. Gastroenterology 116:A381, 1999.

Brand S, **Nishioka NS**. Endoscopic imaging of fluorescence in the esophagus enhanced by aminolevulinic acid for the detection of dysplasia. Annual Meeting of the American Gastroenterololgoy Association, May 15-19, 1999, Orlando, FL.

Brand, S, Bouma, B, Tearney G, Asimellis, G, **Nishioka, NS**. Endoscopic optical coherence tomography (OCT). Research Seminar (Noon Tutorial). Wellman Laboratory of Photomedicine. June 22, 1999, Boston, MA.

Cheng X, **Boas DA**. A hybrid method for three dimensional, quantitative imaging of heterogeneous turbid medium using diffuse light. SPIE/BioS West, Jan. 1999, San Jose, CA.

Cheng X, **Boas DA**. Diffuse optical diffraction tomography in reflectance mode. OSA Annual Meeting, Oct. 8, 1998, Baltimore, MD.

Cingo NA, Soller BR, **Puyana JC**. Multivariate calibration modeling of liver oxygen saturation using near-infrared spectroscopy. SPIE January, 2000.

Cotin SC, Meglan D, Berry PS, Ottensmeyer M, **Dawson SL**. Toward a Common Anatomic Modeling Language for medical simulation. SPIE, Orlando, FL. April 25, 2000.

Cotin S, **Dawson SL**, Meglan D, Shaffer DW, Ferrell, MA, Sherman P. ICTS, an Interventional Cardiology Training System. Medicine Meets Virtual Reality, Newport CA. January 28, 2000.

Dawson, SL. Keynote Lecture: The challenge of medical simulation. SPIE, Orlando, FL. April 25, 2000.

Gaudette RJ, **Boas DA**, Brooks DH, DiMarzio CA, Miller EL. A comparison of linear reconstruction techniques for 3D DPDW imaging of absorption coefficient. SPIE/BioS West, Jan. 1999, San Jose, CA.

Hintz S, Siegel AM, Benaron DA, **Boas DA**. Bedside functional imaging of the premature infant brain during passive motor activation. SPIE/BioS West, Jan. 1999, San Jose, CA.

Hoffman AM. The forced oscillatory mechanics approach to studying the association between baseline and stimulated airway geometries and airway inflammation in horses. *Proc Comp Resp Soc*, Vancouver, BC, 1999.

Hoffman AM. Forced oscillatory mechanics employing an optimal waveform ventilator for measurement in anesthetized sheep with variable elastance. *Proc Comp Resp Soc*, Vancouver, BC, 1999.

Hoffman AM, **Ingenito EP**, Swanson S, Mentzer R, Vin, Kuehne H. Lung mechanics of ovine papain induced emphysema. *Amer Rev Resp Crit Care Med,* 2000: A584.

Ingenito EP, JJ Reilly, K. Lutchen, R Vin, S Swanson, S Mentzer, and A Hoffman. Bronchoscopic volume reduction: an effective and safe alternative to surgical therapy. *Amer Rev Resp Crit Care Med,* 2000:A750.

Kilmer ME, **Boas DA**, Brooks DH, DiMarzio CA, Gaudette RJ, Miller EL. Nonlinear inverse scattering methods for diffuse photon density wave imaging. SPIE/BioS West, Jan. 1999, San Jose, CA.

Ling GSF, Rhee P, Ecklund J.M. In Search of Technological Solutions to Battlefield Management of Combat Casualties (Invited paper) 3712-01.

Ling, GSF, Riechers, RG, Zeidman SM, Rhee P, Wiesmann WP. *In vivo* Validation of a Novel Intracranial Hemorrhage Detector using Microwaves, 3712-02.

Lorigo L, Faugeras O, **Grimson WEL**, Keriven RL, Kikinis R, Westin CF. Co-Dimension 2 Geodesic Active Contours for MRA Segmentation", Int'l Conf. Information Processing in Medical Imaging, Hungary, pp. 126-139, 1999.

Lorigo L, Faugeras O, Grimson WEL, Keriven R, Kikinis R, **Westin CF**. Codimension-Two Geodesic Active Contours. Proc. of IEEE Computer Conference on Computer Vision and Pattern Recognition, pp. 365-374, 2000.

Lorigo L, Faugeras O, Grimson WEL, Keriven RL, Kikinis R, **Westin CF**. Codimension-Two Geodesic Active Contours", Proc Of IEEE Computer Conference on ComputerVision and Pattern Recognition, CVPR' 2000.

Nahum RT, Eroglu A, Toth TL, Perez G, Isaacson K, **Leykin L**. Laser-assisted intracytoplasmic sperm injection in human oocytes. ESHRE, 1999.

Ottensmeyer MP, Ben-Ur E, **Salisbury JK**. Input and output for surgical simulation: devices to measure tissue properties *in vivo* and a haptic interface for laparoscopy simulators. Medicine Meets Virtual Reality, Newport, CA. January 28, 2000.

Perez, AR, Moncure, AC, **Rattner, DW**. Obesity is a Major Cause of Failure for both Transabdominal and Transthoracic Antireflux Operations. Gasteroenterology. 1999; 116:A134-S0210.

Pien, H, Chair/Editor, Proceedings of SPIE – SPIE-The International Society for Optical Engineering, Battlefield Biomedical Technologies April 6, 1999, Orlando, Florida.

Puyana JC, Soller BR, Cingo N, Heard S. Hepatic tissue acidosis and PCO_2 but not PO_2 correlate with liver dysfunction in hemorrhagic shock. Submitted to the American Association of Surgery and Trauma (AAST), October, 2000.

Puyana JC, Soller BR, Cingo N, Heard S, Weismann W. Hepatic acidosis as an end point of resuscitation in hemorrhagic: shock application of near infrared spectroscopy.

59th annual meeting of the American Association for the Surgery of Trauma September 1999, Boston, MA.

Rattner, DW. Improvement of Psychological Well Being and Gastrointestinal Symptoms by Laparoscopic Nissen Fundoplication. Gasteroenterology. 1999; 116:A1343-S0209.

Shaffer DW, Meglan D, Ferrell M, Dawson S. Virtual Rounds: Simulation-based Education in Procedural Medicine. International Society for Optical Engineering (SPIE), April 6, 1999, Orlando, FL.

Shaffer DW. Why a Monkey Can't do it: Simulation Systems and the Development of Clinical Wisdom. SMIT Meeting, Boston, MA, September 1999.

Shaffer DW. Design of Learning Architecture for Medical Simulation. Society for Technology in Anesthesia, Newport Beach, CA, January 2000.

Shaffer DW. Stalking the Wild LAMA: Learning Architecture for Medical Applications. Medicine Meets Virtual Reality, Newport Beach, CA, January 2000.

Shaffer DW. Learning Architecture for Medical Applications. TATRC Integrated Research Team for Medical Modeling and Simulation. Ft. Detrick, MD. February 2000.

Siegel AM, Marota J, Mandeville J, Rosen B, **Boas DA**. Diffuse optical tomography of rat brain function: A comparative study with fMRI. SPIE/BioS West, San Jose, CA. January 1999.

Smith JJ. Regulatory and legal implications of modifying FDA-approved medical devices. J Vasc and Interventional Radiol 11(1):19-23, 2000.

Smith JJ. Physician modification of legally marketed medical devices: regulatory implications under the Food, Drug and Cosmetic Act. Food and Drug Law J 55:245-254, 2000.

Smith JJ, Shyjan AM. Defining "least burdensome means" under the Food and Drug Administration Modernization Act of 1997. Food and Drug Law J (in press) 2000.

Smith JJ. Medicare coverage for new medical technology: the basics of health care financing administration policy. Amer J Roentgenology (in press) 2000.

Smith JJ. Regulation of medical devices in radiology: current standards and future opportunities. Radiology (in press) 2000.

Soller BR, Heard SO, Cingo N, **Puyana JC**. Regional hepatic dysoxia during hemorrhagic shock in swine. Shock 13:(Suppl): 48, 2000.

Soller BR, Heard SO, Khan T, Cingo NA, **Puyana JC**. Muscle pH correlates with hepatic acidosis and injury during swine hemorrhagic shock. Submitted to 30th International Symposium on Critical Care Medicine.

Soller BR, Heard SO, Cingo NA, **Puyana JC**. Hepatic tissue pH and PCO2 indicate successful resuscitation from swine hemorrhagic shock" Submitted to 30th International Symposium on Critical Care Medicine.

Soller BR, Cingo NA, **Puyana JC**. "Simultaneous measurement of liver tissue pH and venous oxygen saturation using NIR spectroscopy and PLS regression", accepted for FACSS 2000 (Federation of Analytical Chemistry and Spectroscopy Societies).

Soller BR, **Puyana JC**, Cingo N, Kahn T, His C, Favreau J, Heard S. "Simultaneous determination of hepatic venous oxygen saturation, hemoglobin and hepatic tissue pH with near infrared spectroscopy during hemorrhagic shock in swine". Presented at the 29th Educational Symposium of the Society of Critical Care Medicine, February 2000.

Soller BR. Spectroscopy and Tissue pH. Presented as part of the Symposium Tissue and Cellular Monitoring at the 29th Educational Symposium of the Society of Critical Care Medicine", February 2000.

Soller BR, Heard SO, Cingo N, **Puyana JC**. Regional hepatic dysoxia during hemorrhagic shock in swine. Submitted to the Shock Society 23rd Annual Conference on Shock, June, 2000.

Soller BR, Cingo N, **Puyana JC**, Heard SO. Hepatic tissue acidosis and PCO2 but not PO2 correlation with liver dysfunction in hemorrhagic shock. Submitted to the AAST October 2000.

Soller BR, **Puyana JC**, Cingo NA, Kahn T, Hse C, Favreau J, Heard S. Simultaneous determination of hepatic venous oxygen saturation, hemoglobin and hepatic tissue pH with near infrared spectroscopy during hemorrhagic shock in swine. 29th Educational Symposium of the Society of Critical Care Medicine, February 2000, Orlando FL.

Soller BR, Zhang S, Micheels RH, **Puyana JC**. Noninvasive NIR Measurement of Tissue pH to assess Hemorrhagic Shock in Swine.

Troulis MJ, **Kaban L.** Minimally Invasive Orthognathic Surgery. 14th International Conference on Oral and Maxillofacial Surgery, Symposium on Congenital and Developmental Craniomaxillofacial Disorders at the Millenium, Washington, DC, April 29, 1999.

Troulis, MJ, Perrott, DH, Seldin, EB, Gordon, J, **Kaban, L**. Endoscopic Approach to the Mandibular Ramus for Placement of Distraction Devices. AAOMS Annual Meeting, September 16-20, 1998, New Orleans, LA.

Troulis MJ, Seldin EB, Glowacki J, Perrot D, Gordon J, **Kaban, L**. Endoscopic Approach to the Mandible for Distraction Osteogenesis. American Cleft Palate Craniofacial Association Meeting, April 20-25, 1998, Baltimore, MD. [Video]

9.0 Appendices

Appendix A. CIMIT Forum Topics -- Year 2

- **Patterns of Technology Adoption: Laparoscopic Cholecystectomy use in Eastern Massachusetts**
- Randall Stafford, MD Massachusetts General Hospital (MGH)

- **The Mechanics of Cell Regulation**
- Donald Ingber, MD, PhD Beth Israel-Deaconess Medical Center

- **Biosense Cardiac Navigation System**
- Ran Kornowski, MD Washington Hospital Center, Washington, DC

- **Economic Evaluation of Medical Technologies: Integrating Large Primary and Secondary Databases**
- Stan Finkelstein, MD & Erine Berndt, PhD, Massachusetts Institute of Technology (MIT)

- **Applications of an Innovative Computer Controlled Portable Ventilator**
- Steven Lisco, MD, Brigham and Women's Hospital (BWH)

- **Aqueous Oxygen: A novel Therapy for Acute Ischemia**
- Paul Zalesky, PhD, TherOx, Inc. Costa Mesa, CA

- **Past and Future Activities in the CIMIT Cardiovascular Focus Area**
- James Muller, MD, MGH and Andrew Selwyn, MD, BWH

- **The Role of Telemedicine in the Management of Acute Stroke**
- Lee Schwamm, MD, MGH

- **Optical Imaging of Near-Infrared (NIR) Fluorescent Molecules to Detect Tumors**
- Ralph Weissleder, MD, PhD, MGH

- **Hypothermia as a Neuroprotectant in Patients with Acute Stroke**
- Albert Lee, MD and Walter Koroshetz, MD, MGH

- **Evaluation of Coronary Stents**
- Richard Kuntz, MD, BWH

- **MRI Models of Tissue Destiny in Human Acute Stroke**
- Alma Gregory Sorensen, MD, MGH

- **Biomedical Engineering Group at the Cleveland Clinic: an Overview**

- J. Frederick Cornhill, PhD, Biomedical Engineering Group at Cleveland Clinic

- **Herpes Simplex Virus for Treatment of Liver Tumors**
- Kenneth Tanabe, MD, MGH

- **Cell Interactive Polymers for Tissue Engineering**
- David Mooney, MD, University of Michigan

- **Image Guided Therapy**
- Ferenc Jolesz, MD, BWH

- **Tactile Imaging and Remote Palpation**
- Robert D. Howe, PhD, Harvard University

- **Optical Coherence Tomography (OCT) for Coronary Arteries**
- Guillermo J. Tearney, MD, PhD, MGH

- **OR of the Future**
- Dennis Adar and Randy Tomaszewwki, Skytron Group, Grand Rapids, MI

- **Progress Report: Tissue Engineering**
- Joseph Vacanti, MD Dept. of Pediatric Surgery, Massachusetts General Hospital (MGH)

- **Molecular Targeting for Pain Therapy using Image Guided Methods**
- David Borsook, MD, PhD Department of Radiology and Neurology, MGH

- **Determination of Endothelial Shear Stress using Intravascular Flow-Profiling to Predict Progression of Coronary Atherosclerosis and Restenosis *In Vivo***
- Peter H. Stone, MD and Charles L. Feldman, ScD Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital (BWH)

- **Diffusion MRI of Tissue Fiber Architecture *In Vivo***
- Van J. Wedeen, MD Department of Radiology, MGH

- **Photochemical Tissue Bonding in the Cornea**
- Louise Mulroy, PhD Wellman Laboratories of Photomedicine, MGH

- **The Art of the Demo**
- Richard Borovoy, PhD Media Laboratory, Massachusetts Institute of Technology, (MIT)

- **Incontinence due to Pelvic Organ Prolapse following Pregnancy**
- Peter L. Rosenblett, MD Dept. of Urogynecology, Mt. Auburn Hospital, Cambridge, MA

- **Problems in the Treatment of Ovarian Cancer**
- Arlan F. Fuller, MD Department of Gynecologic Oncology, MGH

- **Laparoscopic versus Open Gastric Bypass Surgery**
- Janey S. A. Pratt, MD Department of Surgery, MGH

- **Functional Imaging of Cartilage**
- Martha L. Gray, PhD Harvard-MIT Division of Health Sciences and Technology, MIT

- **Outcome Assessment in Menorrhagia**
- Johanna L. Bosch, PhD Decision Analysis and Technology Assessment Group, MGH

- **Robot-Assisted Minimally-Invasive Cardiac Surgery**
- Robert D. Howe, PhD Division of Engineering and Applied Science, Harvard University, Cambridge, MA

- **Progress Report: Computer-Based Medical Simulation**
- Steven L. Dawson, MD Center for Innovative Minimally Invasive Therapy (CIMIT), Partners HealthCare System

- **Digital Telecommunications and the Future of Cities**
- William Mitchell, Dean of the MIT School of Architecture and Planning, Cambridge, MA

- **Pulsed Fluid Waver Laser Vasodilation**
- John W. Peterson, PhD Department of Neurosurgery, MGH

- **Hydroxyapatite Cement: A Novel Biomaterial for Craniofacial Skeletal Tissue Engineering and Reconstruction**
- Craig D. Freidman, MD Fox Chase Center, Philadelphia, PA

- **The Pedagogy of Realistic Medical Simulation**
- James Gordon, MD Department of Emergency Medicine, MGH

- **MRI-Derived Measurements for Routine Monitoring of Brain Lesion Burden in Multiple Sclerosis**
- Charles R. G. Guttman, MD Department of Radiology, BWH

- **Smart Medical Systems Team: National Space Biomedical Research Institute**
- Jeffrey P. Sutton, MD, PhD Neural Systems Group, MGH and Harvard Science and Technology (HST)

- **3D Planning for Distractor Osteogenesis**
- Jaime Gateno, DDS, MD University of Texas Cleft Craniofacial Institute, Houston, TX

- **Noninvasively Measuring Perfusion of Biological Tissue by Blood**
- Derin A. Sherman, PhD, MIT

- **Pilot Single Dose Study of a MMP-2 Specific Near-Infrared Fluorescent Probe in the Detection of Mullerian Tumors**
- Michael Seiden, MD, PhD Division of Hematology/Oncology, MGH

- **Introductory Comments: CIMIT Office of Technology Development**
- Jonathan Jay Rosen, PhD Director, CIMIT Office of Technology Development

- **Special Presentation and Demonstration: Simulation-Based Surgery Training**
- Dwight Meglan, PhD Virtual Presence Inc., Boston, MA

- **Training Inquisitive Physicians: The Harvard PASTEUR Initiative**
- Dennis A. Ausiello, MD Jackson Professor of Clinical Medicine, Harvard Medical School; Physician-in Chief, MGH; Director, PASTEUR

- **Development of a Real-Time, Third Harmonic Microscope with Touch Interaction**
- Jeff Squier, PhD Department of Electrical and Computer Engineering, University of California, San Diego

- **New Models for Supporting Innovation**
- Jonathan Jay Rosen, PhD Director, CIMIT Office of Technology Development

- **Integrating Modern Technology into the Procedure Room of the Future**
- David Rattner, MD Clinical Director, CIMIT

- **A Novel Method to Cool of Rewarm by Means of Hyperventilation with Sulfur Hexafluoride**
- Massimo Ferrigno, MD and Hal Feldman, DSc Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital (BWH), Boston, MA

- **A Computer Based Three-Dimensional Imaging Treatment Planning System to Drive an Endoscopically Placed, Miniature, Facial Skeletal Distraction Device**
- Leonard Kaban, MD, DMD Chief of Oral and Maxillofacial Surgery, Massachusetts General Hospital (MGH) and Peter Everett, Surgical Planning Lab, BWH

- **Interactive Biomaterials for Cell Biology and Tissue Engineering**
- Linda G. Griffith, Department of Chemical Engineering and Division of Bioengineering and Environmental Health, Massachusetts Institute of Technology, Cambridge, MA (MIT)

- **Overview of New Advanced Technology Team**
- Steve Oesterle, MD Department of Cardiology, MGH

- **Development of a Servo-Controlled Microsurgical Laser Scapel Based on Spectroscopic Feedback: The Smart Scapel**
- Colin Brenan, PhD MIT

- **Trauma and Critical Care Program Update**
- Juan Carlos Puyana, MD BWH

- **Knee Arthroscopy Simulation**
- Sarah Gibson, PhD MERL

- **Using Intensity-Modulated Light to Detect Breast Cancer**
- Sergio Fantani, PhD, Assistant Professor, Bioengineering Center, Tufts University, Medford, MA

- **An Interactive Telemedical System for Monitoring Congestive Heart Failure Patients at Home**
- Adrian Urias, Michael Tapper, Elise Lawson and Ryan Stuck Harvey Mudd College

- **Surgical Planning Advanced Technology Team**
- Carl-Fredrik Westin, PhD and Ron Kikinis, MD BWH

- **Minimally Invasive Surgical Techniques for Lower Extremity Revascularization**
- Magruder C. Donaldson, MD Department of Vasculary Surgery, BWH

- **Microbial Pathogen Finger Printing Using a Microarray Biosensor**
- Mark Klempner, MD Professor of Microbiology and Molecular Biology, New Englans Medical Center (NEMC), Boston, MA

- **Medical Simulation: More than just a Black Box**
- David W. Shaffer, PhD CIMIT

- **Bronchoscopic Lung Volume Reduction**
- Edward Ingenito, MD, PhD Pulmonary Division, BWH

- **Surgical Confocal Imaging**
- Matthew White, MD Research Fellow in Otolaryngology/Head and Neck Surgery, Wellman Laboratories of Photomedicine, MGH, Boston, MA

- **Invited Speaker: Simulation and Training**
- Thomas M. Krummel, MD Stanford

- **Regulatory Affairs at CIMIT**
- John J. Smith, MD, JD Director of Regulatory Affairs, CIMIT

- **An Overview of HCFA's National Coverage Decision Process**
- Hugh F. Hill, MD, JD Acting Director, Coverage and Analysis Group, Health Care Financing Administration

- **An Overview of the Field of Tissue Engineering**
- Joseph Vacanti, MD Department of Surgery, MGH and CIMIT

- **An Overview of the Telemedicine and Advanced Technology Research Center**
- Colonel Ronald K. Poropatich, MD Chief of Clinical Applications Division, TATRC, Fort Detrick, MD

- **Imaging for Minimally Invasive Therapy**
- Kirby Vosburgh, PhD Associate Director of Program Development, CIMIT

- **Intraoperative Hormonal Criteria for Success during Parathyroid Surgery**
- Gregory W. Randolph, MD Massachusetts Eye and Ear Infirmary (MEEI), Boston, MA

- **Optical Imaging of the Newborn**
- Barry Kosofsky MD, PhD Department of Neurology, Ellen Grant, MD, Neuroradiology, and Tom Gaudett, MS Department of Radiology, Massachusetts General Hospital (MGH)

- **Panel Discussion: PACS - Past Present Future**
- Ramin Khorasani MD Director, Information Management Systems, Brigham and Women's Hospital (BWH), Keith Dreyer MD Vice Chairman of Radiology/Administration MGH, and Patricia Whelan, PACS Manager, MGH

- **Use of Polyethylene glycol hydrogel for aneurysm sac ablation to prevent endoleak and to treat established endoleak during stent graft repair of abdominal aortic aneurysms in a sheep model**
- Chieh-Min Fan, MD, Departments of Radiology and Vascular Surgery, MGH

- **Orthogonal Polarization Spectral Imaging (OPS Imaging): a new tool for the observation and measurement of the human microcirculation**
- Richard G. Nadeau, Co-Founder and Co-Inventor, Chairman of the Board & Chief Executive Officer, Cytometrics, Inc.

- **A Magnetic Enterescope**
- Gill Pratt, PhD, Department of Electrical Engineering and Computer Science MIT, and Janey Pratt, MD, Department of Surgery MGH

- **Partners HealthCare System Research - and CIMIT as an example of a Paradigm Shift**
- Ronald Newbower, PhD VP for Research Management, Partners HealthCare System Sr. VP for Research and Technology, MGH

- **CIMIT PROGRAM REVIEW 1: Stroke Program**
  Acute Stroke: New Directions in Treatment
- Walter Koroshetz, MD Department of Neurology, R. Gilberto Gonzalez, MD PhD Departments of Neurology and Radiology, Lee Schwamm, MD Department of Neurology and David Boas, PhD Department of Radiology MGH

- **Applications of Microtechnology**
- Martin Schmidt, Ph.D., Director of the Microtechnology Lab, Prof. Charles G. Sodini and Prof. Anantha Chandrakasan Microsystems Technology Laboratories MIT

- **CIMIT PROGRAM REVIEW 2: Trauma and Critical Care/Microsensors**
- Juan Carlos Puyana, M.D. Director of Surgical Critical Care BWH, and Chris Dube, Ph.D., Micromechanical Sensor Development, Draper Laboratory

Appendix B Personnel Receiving Pay

Person	Role
Anderson, Rox, M.D.	Investigator
	Leadership
Asimellis, George, Ph.D.	Research Fellow
Boas, David, M.D.	Principal Investigator
Bouma, Brett E, Ph.D.	Principal Investigator
Brady, Thomas, M.D.	Cardiovascular Team Leader
	Investigator
	New Initiatives Team Leader
	CIMIT Executive Director
Brand, Stephan, M.D.	Research Fellow
Brisman, Jonthan, L., M.D.	Principal Investigator
Carpenter, Janine	Industry Project Coordinator
Cathryn Sundback	Post-Doc Fellow
Chandonnet, Grace	Staff Assistant II
Cho, Unsuk	IS Manager
Cohen, Melissa	Administrative Assistant
Crosby, Janice	Director of Industry Liaison
Dawson, Steven, M.D.	New Initiatives Team Leader
	Director, Simulation
Deutsch, Thomas, Ph.D.	Science Recorder
Emanuel, David, D.D.S. M.D.	Investigator
Fuchs, Julie	Surgical Fellow
Garber, Kelly	Administrative Assistant
Gaudette, Thomas, Ph.D.	Engineer
Gazelle, Scott G., Ph.D.	Principal Investigator
Gesner, Charlotte	Administrative Assistant
Gleason, Suzanne, Ph.D.	Economist
Gonzalez, R, Gilberto M.D. Ph.D.	Stroke Team Leader
	Principal Investigator
Greaves, Kenneth	IS Manager
Greenberg, Steven, M, M.D. Ph.D.	Principal Investigator
Halpern, Elkan F., Ph.D.	Statistician
Hanna, Lamees	Industry Proram Coordinator
Harvey, Susan	Administrative Assistant
Herry-Galloway, Michelle	Administrative Assistant
Humphrey, Ann	Industry Account Manager
Isaacson, Keith, M.D.	Leadership

Jamie Lien	Student
Jang, Ik-Kyung, M.D. Ph.D.	Investigator
	Leadership
Kaban, Leonard B, D.M.D., M.D.	Principal Investigator
Kaihara, Satoshi	Surgical Fellow
Kang, Dong-Heon, M.D.	Investigator
Kelly, Miranda	Administrative Assistant
Kigin, Colleen	Director, Program Development
Kohei Ogawa	Surgical Fellow
Koka, Rahul	Technician
Koroshetz, Walter, M.D.	Stroke Program Team Leader
Lee, Albert, M.D.	Research Scientist
Lester, Jessica, M.M.	Research Associate
Linde, Peter	Surgical Fellow
Maddeford, Jennifer	Staff Assistant
Mandeville, Joseph, M.D.	Medical Staff
Marota, Joseph, M.D.	Medical Staff
McAuliffe, Daniel	Stroke Program Manager
Mckenzie, Sarah, B.A.	Research Assistant
McMahon, Pamela, B.S.	Research Associate
McNaughton-Collins, Mary, M.D.	Outcomes Analyst
Michio Sato	Surgical Fellow
Mohammad-Reza Kaazempur-Mofrad	Post-Doc Fellow
Muller, James, M.D.	Cardiovascular Team Leader
Nishioka, Norman, M.D.	Awards Program Director
	Principal Investigator
Nolan, Marybeth	Administrative Assistant
O'Donnel, Joan, R.N.	Nurse Coordinator
Oesterle, Steven M.D.	ATT Program Team Leader
Osborn, Lynn, R	Director of Admin. and Finance
Pagett, Jane	Financial Analyst
Palumbo, Andrea	Clinical Studies Coordinator
Parrish, John A., M.D.	CIMIT Director
Patel, Shveta, M.D.	Research Assistant
Pien, Homer, Ph.D.	ATT Leader
Puricelli, William, R.N.	Clinical Coordinator
Puyana, Juan Carlos, M.D.	Trauma Team Leader
	Principal Investigator
Raven, Michael	Student
Robichaud, Annette	Finance Administrator
Ryan, Jeanne	Administrative Assistant
Sage, Melanie	Administrative Assistant
Schlendorf, Kelly	Clinical Studies Coordinator
Schomacker, Kevin, Ph.D.	Co-Investigator

Seldin, Edward B, D.M.D.	Investigator
Shaffer, David, Ph.D.	Director
Shishkov, Milen, Ph.D.	Research Fellow
Shulman, Beth	Secretary
Smith, John J., M.D.. J.D.	FDA Activites Director
Solan, Lalan	Research Technician
Sorensen, Alma Gregory, M.D.	Principal Investigator
Stiller, Jane	Administrative Assistant
Strod, Deborah	Technology Associate
Tanabe, Kenneth, M.D.	Cancer Team Leader
Taylor, George	Courier
Terai, Hidetomi	Surgical Fellow
Titus, James	Lab Supervisor
Torchiana, David, F, M.D.	Principal Investigator
Tracy Griksheit	Surgical Fellow
Vacanti, Joseph, M.D.	ATT Team Leader
	Principal Investigator
Vosburgh, Kirby, Ph.D.	Leadership
Weissbach, Karen	Program Specialist
White, Jennifer, M.D.	Research Fellow
Yabushita, Hiaroshi, M.D.	Investigator

Appendix C. Personnel Receiving Degrees

In this year, no personnel supported by CIMIT received graduate degrees.